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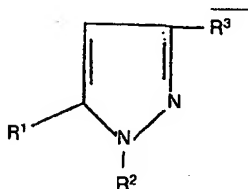
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(54) Pyrazole derivatives and pharmaceutical compositions containing them.

(57) Pyrazole derivatives of the general formula:



7 to 11 carbon atoms and R² represents a hydrogen atom, R³ does not represent -C=O, are novel compounds which

OR⁴

have excellent antilipemic activity with a very low toxicity to humans, and accordingly are suitable for use as pharmaceutical agents in the treatment of lipemia.

wherein R¹ represents an alkyl group of 7 to 17 carbon atoms, R² represents a hydrogen atom, a lower alkyl group or a phenyl group and R³ represents -C=O, -C=O

or -CH₂OH, wherein R⁴ represents a hydrogen atom or a lower alkyl group, R⁵ represents -CH₂CH₂OH or
 -CH₂-C=O,

R⁶

wherein R⁶ represents a hydroxyl group or a lower alkoxy group with a proviso that when R¹ represents an alkyl group

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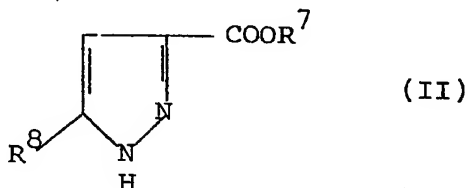
DESCRIPTION"PYRAZOLE DERIVATIVES AND PHARMACEUTICAL COMPOSITIONS
CONTAINING THEM"

The present invention relates to novel pyrazole derivatives having excellent antilipemic activity and suitable for use in the treatment of lipemia.

5 Although several antilipemic pharmaceutical agents have been proposed for use in the treatment of lipemia, they suffer the common defect of exhibiting side effects upon long term administration. For instance, clofibrate which has been widely administered
10 as an antilipemic agent causes diseases in the biliary duct and there is the possibility that clofibrate may cause cancers. Further, pharmaceutical compositions comprising nicotinic acid are only rarely used because of the large dosages required and the side effect of
15 causing flushing and eruptions on the face and skin of the patient being treated.

After synthesizing and testing various compounds we have found that pyrazole derivatives of the general formula (I) shown below have excellent anti-
20 lipemic activity.

Pyrazole derivatives of the general formula (II):



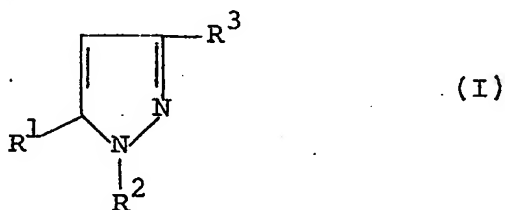
wherein R^7 represents a hydrogen atom or a lower alkyl

group and R^8 represents an alkyl group of 3 to 11 carbon atoms, are known, and their synthesis and their physical- and chemical properties have been reported by Keshin, H et al. (Istanbul Univ. Fen. Fak. Mecum. Seric., 34, 95-108, 1969), but without mention of any pharmacological properties.

Although Kupiecki F. et al reported that 5-methylpyrazole-3-carboxylic acid can reduce the level of lipid in human blood (refer to J. Pharmacol. Expt. Therap., 160, 166, 1968), Lang P.D. et al subsequently reported that its clinical effectiveness was not decisive and its use caused side effects such as hypoglycemia, rendering it unsuitable for use in treating lipemia (refer to Arzneim. Forsch., 25(1), 117, 1975).

Accordingly, the fact that the pyrazole derivatives of the present invention have excellent antilipemic activity and that they could safely be used in the treatment of lipemia was not to be expected from the prior art.

The pyrazole derivatives of the present invention are represented by the general formula (I)



wherein R^1 represents an alkyl group of 7 to 17 carbon atoms, R^2 represents a hydrogen atom, a lower (preferably C_1-C_4) alkyl group or a phenyl group, R^3 represents $-C(=O)OR^4$, $-C(=O)NH-R^5$ or $-CH_2OH$ wherein R^4

represents a hydrogen atom or a lower (preferably

C_1-C_4) alkyl group, R^5 represents $-CH_2CH_2OH$ or
 $-CH_2-\underset{\substack{| \\ R^6}}{C=O}$ wherein R^6 represents a hydroxyl group or

a lower (preferably C_1-C_4) alkoxy group, with the
 proviso that when R^1 represents an alkyl group of 7 to
 5 11 carbon atoms and R^2 represents a hydrogen atom, R^3
 does not represent $-\underset{\substack{| \\ OR^4}}{C=O}$.

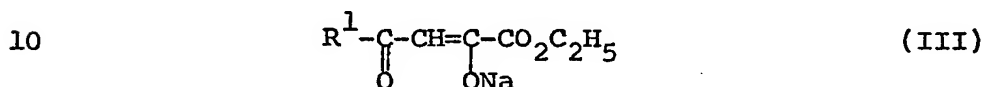
Examples of pyrazole derivatives of
 formula (I) (hereinafter referred to as the present
 pyrazole derivatives) are: 5-n-tridecylpyrazole-3-
 10 carboxylic acid, 5-n-pentadecylpyrazole-3-carboxylic
 acid, 5-n-heptadecylpyrazole-3-carboxylic acid, ethyl
 5-n-tridecylpyrazole-3-carboxylate, ethyl 5-n-penta-
 decylpyrazole-3-carboxylate, ethyl 5-n-heptadecyl-
 pyrazole-3-carboxylate, 3-N-2'-hydroxyethylcarbamoyl-
 15 5-n-nonylpyrazole, 3-N-2'-hydroxyethylcarbamoyl-5-n-
 undecylpyrazole, 3-N-2'-hydroxyethylcarbamoyl-5-n-
 tridecylpyrazole, 3-N-hydroxycarbonylmethylcarbamoyl-
 5-n-nonylpyrazole, 3-N-hydroxycarbonylmethylcarbamoyl-
 5-n-undecylpyrazole, 3-N-hydroxycarbonylmethyl-5-n-
 20 tridecylpyrazole, 3-N-ethoxycarbonylmethylcarbamoyl-5-
 n-nonylpyrazole, 3-N-ethoxycarbonylmethylcarbamoyl-5-
 n-undecylpyrazole, 3-N-ethoxycarbonylmethylcarbamoyl-
 5-n-tridecylpyrazole, 3-hydroxymethyl-5-n-tridecyl-
 pyrazole, 3-hydroxymethyl-5-n-heptylpyrazole,
 25 3-hydroxymethyl-5-n-nonylpyrazole, 3-hydroxymethyl-5-n-
 undecylpyrazole, 1-methyl-5-n-tridecylpyrazole-3-
 carboxylic acid, 1-methyl-5-n-heptapyrazole-3-carboxylic
 acid, 1-methyl-5-n-nonylpyrazole-3-carboxylic acid,
 1-methyl-n-undecylpyrazole-3-carboxylic acid, 1-phenyl-
 30 5-n-nonylpyrazole-3-carboxylic acid, 1-phenyl-5-n-
 heptylpyrazole-3-carboxylic acid, 1-phenyl-5-n-undecyl-

pyrazole-3-carboxylic acid and 1-phenyl-5-n-tridecyl-pyrazole-3-carboxylic acid.

The present pyrazole derivatives can be synthesized by the following methods:

- 5 (1) Syntheses of 5-alkylpyrazole-3-carboxylic acids and esters thereof:

A sodium enolate of the general formula (III) obtainable by a Claisen condensation reaction between a higher-alkyl methyl ketone and diethyl oxalate:



wherein R^1 is as defined for formula (I), is reacted with hydrazine hydrate in a mineral acid for 4 to 10 hours with heating and stirring under reflux to provide an ethyl ester of a 5-alkylpyrazole-3-carboxylic acid.

- 15 The corresponding acid can be obtained by hydrolyzing the ethyl ester with sodium hydroxide in an aqueous lower alcoholic solution at a temperature around 100°C , or by reacting a sodium enolate (III) with hydrazine sulfate in an aqueous lower alcoholic solution
20 of sodium hydroxide with heating under reflux for 2 to 3 hours.

- (2) Synthesis of 5-alkylpyrazol-3-carboxamides:

- A sodium enolate of formula (III) is heated with hydrazine sulfate in an aqueous solution of sodium
25 hydroxide for 2 to 3 hours, and the reaction product is brought into reaction with thionyl chloride to provide a 5-alkylpyrazol-3-carboxylic acid chloride. The acid chloride is then reacted with an amine derivative of the general formula, NH_2-R^5 , wherein R^5 represents a
30 group $-\text{CH}_2\text{CH}_2\text{OH}$ or a group $-\text{CH}_2\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{R}^6$, wherein R^6 is a hydroxyl group or a lower alkoxy group, or a hydrochloride thereof, in dichloroethane in the presence of triethyl-

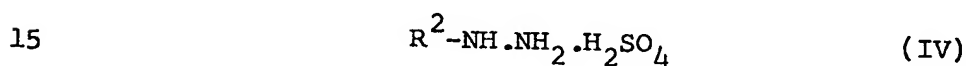
amine to provide the desired compound.

(3) Synthesis of 3-hydroxymethyl-5-alkylpyrazoles:

A sodium enolate of formula (III) is reacted with hydrazine hydrate in a mineral acid with heating for 4 to 10 hours under reflux to provide an ethyl-5-alkylpyrazole-3-carboxylate, which is reduced with lithium aluminum hydride in anhydrous tetrahydrofuran to provide a 3-hydroxymethyl-5-alkylpyrazole.

(4) Synthesis of 1-alkyl-5-alkylpyrazole-3-carboxylic acids:

A sodium enolate of formula (III) is dissolved in distilled water or methanol together with a mono-substituted hydrazine sulfate of the general formula (IV):



wherein R^2 represents alkyl of 1 to 3 carbon atoms, and to the thus obtained solution an aqueous solution of sodium hydroxide is added, and then the mixture is heated for 1 to 2 hours to provide the desired product.

(5) Synthesis of 1-phenyl-5-n-alkylpyrazole-3-carboxylic acids:

A sodium enolate of formula (III) is dissolved in distilled water or methanol together with phenylhydrazine sulfate, and to the thus obtained solution an aqueous solution of sodium hydroxide is added, and then the mixture is heated for 1 to 2 hours to provide the desired products.

The synthesis of various pyrazole derivatives of formula (I) and their physical- and chemical properties will be described below in Examples 1 to 25. Before that an explanation will be provided of the pharmacological properties of the present pyrazole derivatives:

Pharmacological tests were carried out on each compound of the present pyrazole derivatives using

nicotinic acid for comparison.

(i) Pharmacological test against hypertriglyceridemia:

Seven groups of male SD rats, each group
5 consisting of 6 animals, were used as test animals and
one group consisting of 12 animals was used as a control.
The test groups were made hypertriglyceridemic by
administering aqueous 10% by weight solution of fructose
for 2 days, while the animals of the control group were
10 given tap water. The administration to the test groups
of six pyrazole derivatives and of nicotinic acid was as
follows:

Each pyrazole derivative and nicotinic acid
was separately dissolved or dispersed in an aqueous 1%
15 solution of carboxymethylcellulose (CMC) at a
predetermined concentration, and the thus prepared
solution or dispersion was orally administered in three
doses, each dose having a volume of 0.5 ml/100 g body
weight, a first dose just after the commencement of the
20 test, a second dose 24 hours after the first dose, and
a third dose 18 hours after the second dose. The total
dosage of each compound was such that each animal received
300 mg/kg of each compound as free carboxylic acid. The
rats of the control group were given the aqueous 1%
25 solution of CMC only, in three doses at the same
intervals as the test groups. All the groups were fed
with the same diet during the test period.

After 48 hours of the commencement of the test,
a blood sample was collected from each animal by
30 amputation of the carotid artery, and serum was separated
from the blood sample and frozen to be kept until lipid
analysis.

Lipid analysis:

Serum triglyceride was determined by Acetyl-

acetone Method, and the reduction percentage of lipid was calculated on the basis of the following formula:

$$(1 - \frac{\text{amount of triglyceride in serum of test animal}}{\text{amount of triglyceride in serum of control}}) \times 100$$

5 = the reduction percentage of lipid

wherein the reduction percentage is the average for the test animals in each group.

Analysis for serum cholesterol:

10 The content of serum cholesterol was determined by an enzymatic method using cholesteroxidase, and the reduction percentage of cholesterol was calculated according to the following formula:

$$(1 - \frac{\text{amount of cholesterol in serum of test animal}}{\text{amount of cholesterol in serum of control}}) \times 100$$

15 = the reduction percentage of cholesterol

The results of the analyses are shown in Table 1.

TABLE 1

Compound	Total Dose (mg/kg)	Reduction Percentage	
		Triglyceride	Cholesterol
5-n-tridecylpyrazole-3-carboxylic acid	300	76.4	59.8
5-n-pentadecylpyrazole-3-carboxylic acid	300	62.8	32.1
5-n-heptadecylpyrazole-3-carboxylic acid	300	30.5	24.5
Ethyl 5-n-tridecylpyrazole-3-carboxylate	329	88.0	65.1
Ethyl 5-n-pentadecylpyrazole-3-carboxylate	326	67.8	34.1
Ethyl 5-n-heptadecylpyrazole-3-carboxylate	324	35.2	32.9
3-hydroxymethyl-5-tridecylpyrazole	300	78.2	55.8
3-n-ethoxycarbonylmethylcarbamoyl-5-tridecylpyrazole	300	81.4	34.8
1-methyl-5-n-tridecylpyrazole-3-carboxylic acid	300	75.9	61.2
Nicotinic acid	300	24.1	16.4

(ii) Pharmacological test against hyper-cholesterolemia:

Three groups of male SD rats each weighing about 150g, each group consisting of five rats, were used as test animals and one group consisting of 10 rats was used as control. All animals were fed a high cholesterol diet consisted of 1% cholesterol, 0.2% sodium cholate, 5% olive oil and commercial diet up to total 100% for 7 days. The test compounds of the present invention and clofibrate, as a medicine for comparison, were respectively dissolved or dispersed in an aqueous 1% solution of CMC so that the volume of the solution or dispersion administered each time to an animal was 0.5 ml/100g body weight, and the solution or dispersion was orally administered so that the amount of administration each time of each pyrazole derivative or of clofibrate was 200 mg/kg body weight. Administration was carried out once a day for 7 consecutive days. Water was taken ad lib. After 20 hours of fasting from the last administration, a blood sample was taken from each animal by amputation of the carotid artery, and the serum separated was frozen until the analysis of cholesterol shown as follows:

Cholesterol analysis

The content of serum cholesterol was determined by the above-mentioned method. The beta-lipoprotein-cholesterol was determined by "heparin-calcium precipitation method". The reduction percentage of cholesterol in serum and beta-lipoprotein were calculated in the same manner as above. The results are shown in Table 2.

TABLE 2

	Compound	Dose (mg/ kg/day)	Reduction Percentage	
			Cholesterol	Cholesterol in beta- lipoprotein
5	5-n-tridecylpyrazole- 3-carboxylic acid	200	45.2	54.3
	3-hydroxymethyl- 5-n-tridecylpyrazole	200	52.7	25.2
10	3-n-ethoxycarbonyl- methylcarbamoyl-5- n-tridecylpyrazole	200	48.6	32.7
15	1-methyl-5-n-tridecyl- pyrazole-3-carboxylic acid	200	60.1	57.3
	Clofibrate	200	- 3.5	- 2.0

As seen from Tables 1 and 2, the present pyrazole derivatives have an excellent antilipemic activity superior to that of nicotinic acid and clofibrate, known antilipemic agents.

The acute toxicity of the present pyrazole derivatives to mammals was determined by the following method. The results showed that each of the present pyrazole derivatives had a LD₅₀ value over 5.0 g/kg body weight significantly larger than that of nicotinic acid, 4.5 g/kg.

Test method for acute toxicity:

Male ICR mice of body weight 21 to 25 g were

divided into several groups each consisting of 8 animals and were fasted for 17 to 18 hours and then orally given a pyrazole derivative or nicotinic acid dissolved or dispersed in an aqueous 1% CMC solution at a rate of 0.2 ml/10 g body weight. The administered amount of each compound was 2.5 g/kg body weight or 5.0 g/kg, and from the mortalities at both levels, LD₅₀ was roughly calculated and compared with LD₅₀ of nicotinic acid.

The following description is an explanation of formulating the present pyrazole derivatives into pharmaceutical compositions. In general, the present pyrazole derivative can be formulated into a pharmaceutical composition of dose unit form by known techniques. Since a present pyrazole derivative is generally administered orally, it is preferably formulated into tablets or capsules. When formulating a present pyrazole derivative into the dose unit form, vehicles, disintegrating agents, binding agents and lubricating agents which are used widely in the pharmaceutical field may be used.

The dose level of the present pyrazole derivative naturally depends upon the degree of hyperlipemia, but, in general, a suitable daily oral dose will be 0.2 to 3.0 g/60 kg of body weight, preferably 0.5 to 1.5 g/60 kg body weight.

Examples 1 to 25 which follow provide a more detailed explanation of the synthesis of the pyrazole derivatives, while Examples 26 and 27 describe their formulation.

EXAMPLE 1

Synthesis of ethyl 5-n-tridecylpyrazole-3-carboxylate: 10.4 g (0.45 mol) of metallic sodium was dissolved in 500 ml of anhydrous ethanol and then
 5 a liquid mixture consisting of 100 g (0.44 mol) of methyl n-tridecyl ketone and 64 g (0.44 mol) of diethyl oxalate was slowly dropped into the solution with stirring. After the addition, the mixture was heated for 5 hours at a temperature of 60°C under stirring.
 10 Then, the reaction mixture was cooled by iced water, and the resulting yellow precipitate was collected by filtration and recrystallized from ethanol to provide 103.3 g (0.1 mol) of sodium 1-ethoxycarbonyl-3-oxo-1-hexadecenolate, $\text{CH}_3(\text{CH}_2)_{12}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}-\text{CH}=\text{C}-\overset{\text{ONa}}{\underset{\text{O}}{\text{C}}}\text{OC}_2\text{H}_5$, as pale yellow
 15

crystals melting at 68 - 70°C at a yield of 67.5%.

To a solution of 34.8 g (0.1 mol) of the sodium 1-ethoxycarbonyl-3-oxo-1-hexadecenolate in 23 ml of glacial acetic acid 5.5 g (0.11 mol) of hydrazine hydrate
 20 was slowly dropped under cooling with iced water. After heating the mixture for 8 hours under reflux, the reaction mixture was cooled and poured into iced water, then neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with benzene.
 25 The separated benzene layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and then dried over anhydrous sodium sulfate. Solvent was evaporated and the residue was recrystallized from ethyl ether to provide 22.6 g of ethyl 5-n-tridecylpyrazole-3-carboxylate as colourless needle-like crystals melting
 30 at 45-46°C at a yield of 70.0%.

Elementary analysis:

found : 70.76% C; 10.66% H; 8.67% N calcd.

as $\text{C}_{19}\text{H}_{34}\text{O}_2\text{N}_2$: 70.76% C; 10.63% H; 8.69% N.

Infra-red absorption spectrum (hereinafter referred to

as IR):

(nujol method)

$\nu_{\text{max}}^{\text{nujol}}$ 3200 - 3100 cm^{-1} (νNH) and 1715 cm^{-1} ($\nu\text{C=O}$).

Mass spectrum (hereinafter referred to as Mass):

m/e 322 (M^+)

Nuclear magnetic resonance spectrum (hereinafter

5 referred to as NMR): (in CDCl_3) δ :

0.87 [3 H, t, $J=6\text{Hz}$, CH_3 CH_2)₁₂]

1.2 - 1.5 [23H, $\text{CH}_3(\text{CH}_2)_{10}(\text{CH}_2)_2$, $\text{CH}_3\text{CH}_2\text{OCO}$]

1.7 (2H, m, $\text{C}_{11}\text{H}_{23}\text{CH}_2\text{CH}_2$)

2.70 (2 H, t, $J=8\text{Hz}$, $\text{C}_{12}\text{H}_{25}\text{CH}_{12}$)

10 4.38 (2 H, q, $J=7\text{Hz}$, $\text{CH}_3\text{CH}_2\text{OCO}$)

6.60 (1 H, s, H in the pyrazole ring)

11.95 (1H, br, NH which disappears by treating with D_2O).

EXAMPLE 2

15 Synthesis of 5-n-tridecylpyrazole-3-carboxylic acid:

A solution of 10 g (0.031 mol) of ethyl 5-n-tridecylpyrazole-3-carboxylate in 50 ml of a 5% methanolic solution of sodium hydroxide was heated under reflux for 5 hours. After adding distilled water, methanol was evaporated under a reduced pressure and the residue was made acidic (pH of about 2) by adding concentrated hydrochloric acid. The separated precipitate was collected by filtration and recrystallized from ethanol to provide 7.2 g of 5-n-tridecylpyrazole-3-carboxylic acid as needle-like crystals melting at 141 - 143°C, a yield of 79.2%.

Elementary analysis:

found : 65.31% C; 9.47% H; 9.58% N.

calcd. as $\text{C}_{17}\text{H}_{30}\text{O}_2\text{N}_2$: 65.35% C; 10.32% H; 8.97% N.

30 IR (KBr-method):

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$\nu_{\text{max}}^{\text{KBr}}$ 3240 cm^{-1} (br. νCH , NH), 3000 - 2300 cm^{-1}
 (br. νNH_2 and CO_2H) and 1680 cm^{-1} ($\nu\text{C=O}$)

Mass : m/e : 294 (M^+)

NMR (in d_6 -DMSO) δ :

- 5 0.85 (3H, t, J=6 Hz, $\text{CH}_3(\text{CH}_2)_{12}$)
- 1.2 - 1.5 (20H, br. s, $\text{CH}_3(\text{CH}_2)_{10}(\text{CH}_2)_2$)
- 1.60 (2H, m, $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{CH}_2$)
- 2.59 (2H, t, J=8 Hz, $\text{CH}_3(\text{CH}_2)_{11}\text{CH}_2$)
- 4.72 (2H, br. NH and CO_2H , which disappears by
 10 treatment with D_2O)
- 6.35 (1H, s, H in pyrazole ring)

EXAMPLE 3

Synthesis of 5-n-tridecylpyrazole-3-carboxylic acid:

- 15 After dissolving 20 g (0.0575 mol) of sodium
 1-ethoxycarboxyl-3-oxo-1-hexadecenolate and 8.2 g
 (0.0633 mol) of hydrazine sulfate in 40 ml of methanol
 with agitation under warming, 11.5 ml of an aqueous 33%
 solution of sodium hydroxide were added dropwise into
 20 the solution. After the addition, the mixture was
 heated for 2 hours under reflux and methanol was
 evaporated after adding distilled water. After making
 the pH of the residue nearly to 2 with concentrated
 hydrochloric acid, water was completely removed by
 25 distillation under a reduced pressure, and the residue
 was extracted with 500 ml of hot acetone. After drying
 the acetonic extract and removing the solvent, the
 residue was recrystallized from ethanol to provide
 5-n-tridecylpyrazole-3-carboxylic acid as colourless in
 30 a yield of 67.4%.

The physical properties of the product were identical to those of the product prepared in Example 2.

EXAMPLE 4

5 Synthesis of ethyl 5-n-pentadecylpyrazole-3-carboxylate:

5.5 g of hydrazine hydrate was dropped slowly into a solution of 40.0 g (0.106 mol) of sodium 1-ethoxycarbonyl-3-oxo-1-octadecenolate in 20 ml of
10 glacial acetic acid under cooling with iced water. After heating the mixture for 5 hours under reflux, the reaction mixture was cooled and poured into iced water and then neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with benzene.
15 After washing the benzene layer with a saturated aqueous solution of sodium hydrogen carbonate and drying over anhydrous sodium sulfate, the solvent was removed by distillation under a reduced pressure. The residue was recrystallized from ethanol to provide 13.4 g of
20 ethyl 5-n-pentadecylpyrazole-3-carboxylate as colourless plate-like crystals melting at 53 to 54°C in a yield of 36.4%.

Elementary analysis:

found : 72.03% C; 11.25% H; 7.74% N.

25 calcd. as $C_{21}H_{38}O_2N_2$: 71.95% C; 10.93% H; 7.99% N.

IR :

$\nu_{\text{max}}^{\text{nujol}}$ 3200 - 3100 cm^{-1} (νNH) and 1718 cm^{-1} ($\nu\text{C} = \text{O}$)

Mass : m/e 350 (M^+)

NMR (in CDCl_3) δ :

30 0.92 (3H, t, J=6 Hz, $\text{CH}_3(\text{CH}_2)_{14}$)

1.2 - 1.6 (27H, $\text{CH}_3(\text{CH}_2)_{12}(\text{CH}_2)_2$ and $\text{CH}_3\text{CH}_2\text{OCO}$)

1.7 (2H, m, $\text{C}_{13}\text{H}_{27}\text{CH}_2\text{CH}_2$)

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2.90 (2H, t, J=8 Hz, $C_{14}H_{29}\underline{CH_2}$)4.72 (2H, q, J=8 Hz, $CH_3\underline{CH_2}OCO$)

7.05 (1H, s, H in the pyrazole ring)

12.35 (1H, br, NH which disappears by treatment
5 with D_2O)EXAMPLE 5

Synthesis of 5-n-pentadecylpyrazole-3-carboxylic acid:

A solution of 13.0 g (0.037 mol) of ethyl
10 5-n-pentadecylpyrazole-3-carboxylate in 100 ml of an
aqueous 5% ethanolic solution of sodium hydroxide was
heated for 7 hours under reflux. After adding
distilled water, ethanol was evaporated by distillation
under a reduced pressure. The residue was made acidic
15 (pH of nearly 2) with concentrated hydrochloric acid,
and then the deposited pale yellow needle-like crystals
were collected by filtration and recrystallized from
ethanol to provide 5-n-pentadecylpyrazole-3-carboxylic
acid as colourless needle-like crystals melting at
20 133 - 135°C in an amount of 6.7 g corresponding to a
yield of 56.0%.


Elementary analysis:

found: 67.34% C; 10.57% H; 8.08% N.

calcd. as $C_{19}H_{34}O_2N_2 \cdot H_2O$:

25 67.01% C; 10.66% H; 8.23% N.

IR:

 $\nu_{\text{max}}^{\text{KBr}}$ 3240 cm^{-1} (br, ν_{NH} , OH), 3000 - 2300 cm^{-1} (br, ν_{NH_2+} and COOH) and 1710 cm^{-1} ($\nu_{\text{C}} = \text{O}$)Mass: m/e 322 (M^+)30 NMR (in d_6 -DMSO) δ :0.86 (3H, t, J=7 Hz, $\underline{CH_3}(CH_2)_{14}$)BAN ORIGINAL 

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- 1.2 - 1.5 (24H, br. s, $\text{CH}_3(\text{CH}_2)_{12}(\text{CH}_2)_2$)
 1.60 (2H, m, $\text{C}_{13}\text{H}_{27}\text{CH}_2\text{CH}_2$)
 2.64 (2H, t, $J=8$ Hz, $\text{C}_{14}\text{H}_{29}\text{CH}_2$)
 6.50 (1H, s, H in the pyrazole ring)
 5 10.60 (2H, br, NH and CO_2H which disappears by treatment with D_2O .)

EXAMPLE 6

Synthesis of ethyl 5-n-heptadecylpyrazole-3-carboxylate:

- 10 3.2g (0.066 mol) of hydrazine hydrate was dropped slowly into a solution of 24.2g (0.06 mol) of sodium 1-ethoxycarbonyl-3-oxo-1-eicosenolate in 13 ml of glacial acetic acid under cooling with iced water. After heating the mixture for 2 hours under reflux,
 15 the reaction mixture was poured into iced water and then was neutralized by a saturated aqueous solution of sodium hydrogen carbonate and extracted with benzene. The benzene layer was washed with a saturated aqueous solution of sodium hydrogen carbonate and dried over
 20 anhydrous sodium sulfate. After removing the solvent by distillation under a reduced pressure, the residue was recrystallized from ethyl ether to provide ethyl 5-n-heptadecylpyrazole-3-carboxylate as colourless needle-like crystals melting at $56 - 57^\circ\text{C}$ in an amount of
 25 13.7g corresponding to a yield of 65.2%.

Elementary analysis:

found : 72.78% C; 11.25% H; 9.58% of N.

calcd. as $\text{C}_{23}\text{H}_{42}\text{O}_2\text{N}_2$: 72.96% C; 11.18% H; 8.97% N.

IR:

- 30 $\nu_{\text{max}}^{\text{nujol}}$ 3200 - 3100 cm^{-1} (νNH) and 1715 cm^{-1} ($\nu\text{C} = \text{O}$)

Mass: m/e 378 (M^+)

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NMR (in d_6 -CDCl₃) δ :0.90 (3H, t, $J = 6$ Hz, $\underline{\text{CH}_3}(\text{CH}_2)_{16}$)1.2 - 1.5 (31H, $\text{CH}_3\underline{(\text{CH}_2)_{14}}(\text{CH}_2)_2$ and $\underline{\text{CH}_3}\text{CH}_2\text{OCO}$)1.7 (2H, m, $\text{C}_{15}\text{H}_{31}\underline{\text{CH}_2\text{CH}_2}$)5 2.55 (2H, t, $J = 8$ Hz, $\text{C}_{16}\text{H}_{33}\underline{\text{CH}_2}$)4.30 (2H, q, $J = 7$ Hz, $\text{CH}_3\underline{\text{CH}_2}\text{OCO}$)5.95 (1H, br, NH which disappears by treatment
with D₂O)

6.45 (1H, s, H in the pyrazole ring).

10 EXAMPLE 7Synthesis of 5-n-heptadecylpyrazole-3-
carboxylic acid:

By the same procedures as in Example 2 ethyl
5-n-heptadecylpyrazole-3-carboxylate (0.026 mol) was
15 hydrolyzed to the corresponding free acid. The crude
pale yellow precipitate was recrystallized from ethanol
to provide 6.8g of colourless needle-like crystals
melting at 125 - 127°C. The yield was 69.5%.

Elementary analysis:

20 found : 69.02% C; 10.55% H; 7.89% N

calcd. as $\text{C}_{21}\text{H}_{38}\text{O}_2\text{N}_2 \cdot \text{H}_2\text{O}$: 68.43% C; 10.94% H;
7.60% N.

IR:

 $\nu_{\text{max}}^{\text{KBr}}$ at 3240 cm^{-1} (br. νNH , OH), 3000 - 2300 cm^{-1} 25 (br. νNH_2^+ and COOH) and 1680 cm^{-1} ($\nu\text{C} = \text{O}$).Mass: m/e 350 (M^+).NMR (in d_6 -DMSO) δ :0.85 (3H, t, $J = 7$ Hz, $\underline{\text{CH}_3}(\text{CH}_2)_{16}$)1.2 - 1.7 (30H, br. s, $\text{CH}_3\underline{(\text{CH}_2)_{15}}\text{CH}_2$)

- 19 -

2.65 (2H, t, $J = 7$ Hz, $C_{16}H_{33}\underline{CH_2}$)

6.48 (1H, s, H in the pyrazole ring)

7.60 (2H, br. NH and CO_2H which disappear by treatment with D_2O)5 EXAMPLE 8

Synthesis of 3-N-2-hydroxyethylcarbamoyl-5-n-nonylpyrazole:

10 An excess of thionyl chloride was added to 2.5g (0.011 mol) of 5-n-nonylpyrazole-3-carboxylic acid and after heating the mixture for 2 hours under agitation at 42 to 43°C, the reaction mixture was condensed to solid under a reduced pressure to obtain 5-n-nonylpyrazole-3-carboxylic acid chloride as yellow crystals.

15 A solution of 0.013 mol of ethylamine and 1.1g (0.011 mol) of triethylamine in 70 ml of dichloroethane was slowly dropped into the acid chloride under cooling with iced water. After agitating the mixture for 8 hours at room temperature, the thus
20 deposited triethylamine hydrochloride was removed by filtration, and iced water was added to the filtrate. The organic phase was separated and dried over anhydrous sodium sulfate, and the solvent therein was distilled off to obtain a residue, which was recrystallized from
25 acetone to provide the desired product as colourless needle-like crystals melting at 48 - 50°C in an amount of 1.6g corresponding to a yield of 51.8%.

Elementary analysis:

found: 61.85% C; 9.47% H and 14.47% N
30 calcd. as $C_{15}H_{27}O_2N_3 \cdot 1/2 H_2O$:
62.04% C; 9.72% H and 14.47% N.

IR:

$\nu_{\text{max}}^{\text{nujol}}$ 3400 - 3000 cm^{-1} (ν_{NH} , OH) and 1625 and 1550 cm^{-1} (ν amide).

- 20 -

Mass : m/e 281 (M^+).NMR (in $CDCl_3$) δ :0.86 (3H, t, $J = 6$ Hz, $\underline{CH_3}(CH_2)_8$)1.2 - 1.5 (12H, br. s, $\underline{CH_3}(CH_2)_6(CH_2)_2$)5 1.6 (2H, m, $C_7H_{15}\underline{CH_2}CH_2$)2.62 (2H, t, $J = 7$ Hz, $C_8H_{17}\underline{CH_2}$)3.38 and 3.55 (2H each, m, $OCNHCH_2\underline{CH_2}OH$)

5.4 (1H, s, H in the pyrazole ring)

8.10 (1H, t-like, $OCNH\underline{CH_2}$)10 EXAMPLE 9

Synthesis of 3-N-2'-hydroxyethylcarbamoyl-5-n-undecylpyrazole:

By the same procedures as in Example 8, 3.0g (0.11 mol) of 5-n-undecylpyrazole-3-carboxylic
 15 acid was transformed to the corresponding amide of hydroxyethylamine. The crude produce was recrystallized from acetone to provide the desired product as colourless needle-like crystals melting at 63 - 65°C in an amount of 1.3g corresponding to a yield
 20 of 38.3%.

Elementary analysis:

found : 66.09% C; 10.19% H and 13.28% N

calcd. as $C_{17}H_{31}O_2N_3$:

65.95% C; 10.10% H and 13.58% N.

25 IR:

$\nu_{\max}^{\text{nujol}}$ 3400 - 3000 cm^{-1} (ν_{NH} and OH) and 1630 and 1560 cm^{-1} (ν amide).

Mass: m/e 309 (M^+)NMR (in $CDCl_3$) δ :30 0.86 (3H, t, $J = 6$ Hz, $\underline{CH_3}(CH_2)_{10}$)

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- 1.2 - 1.5 (16H, br. s, $\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{CH}_2$)
- 1.6 (2H, m, $\text{C}_9\text{H}_{19}\text{CH}_2\text{CH}_2$)
- 2.60 (2H, t, $J = 7 \text{ Hz}$, $\text{C}_{10}\text{H}_{21}\text{CH}_2$)
- 3.55 and 3.75 (2H each, m, $\text{OCNHCH}_2\text{-CH}_2\text{OH}$)
- 5 6.50 (1H, s, H in the pyrazole ring)
- 7.20 (2H, br. NH and OH which disappears by treatment with D_2O)
- 8.10 (1H, br. NH which disappears by treatment with D_2O)

10 EXAMPLE 10

Synthesis of 3-N-2-hydroxyethylcarbamoyl-5-n-tridecylpyrazole:

- By the same procedures as in Example 8, 4.0g (0.014 mol) of 5-n-tridecylpyrazole-3-carboxylic
- 15 acid was transformed to the corresponding amide of hydroxyethylamine. The crude product was recrystallized from acetone to provide colourless needle-like crystals of the desired product melting at $78 - 79^\circ\text{C}$ in an amount of 2.1g corresponding to a yield of 45.1%.

20 Elementary analysis:

found : 67.51% of C, 10.16% of H and 12.20% of N
 calcd. as $\text{C}_{19}\text{H}_{35}\text{O}_2\text{N}_3$: 67.61% of C, 10.45% of H and 12.45% of N.

IR:

- 25 \checkmark ^{nujol}_{max} $3400 - 3000 \text{ cm}^{-1}$ (\checkmark NH and OH) and 1635 and 1555 cm^{-1} (\checkmark amide).

Mass : m/e 337 (M^+).NMR (in CDCl_3) δ :

- 0.87 (3H, t, $J = 6 \text{ Hz}$, $\text{CH}_3(\text{CH}_2)_{12}$)
- 30 1.2 - 1.5 (2H, br. s, $\text{CH}_3(\text{CH}_2)_{10}(\text{CH}_2)_2$)
- 1.6 (2H, m, $\text{C}_{11}\text{H}_{23}\text{CH}_2\text{-CH}_2$)

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2.60 (2H, t, J = 7 Hz, C₁₂H₂₅ - CH₂)3.55 and 3.80 (2H each, m, CONH-CH₂-CH₂-OH)5.0 (2H, br. NH and OH which disappears by treatment with D₂O)

5 6.38 (1H, s, H in the pyrazole ring)

7.84 (1H, br. NH which disappears by treatment with D₂O)EXAMPLE 11

Synthesis of 3-N-ethoxycarbonylmethylcarbamoyl-
10 5-n-nonylpyrazole:

An excess of thionyl chloride was added to
3.1g (0.031 mol) of 5-n-nonylpyrazole-3-carboxylic acid,
and after heating the mixture for 3 hours at 42 to 43°C
with agitation, the reaction mixture was condensed to a
15 solid under a reduced pressure, and the thus formed
5-n-nonylpyrazole-3-carboxylic acid chloride was
dissolved in 25 ml of dichloroethane. This solution was
slowly added dropwise to a mixture of 2.0g (0.014 mol)
of ethyl ester of glycine hydrochloride, 10 ml of
20 triethylamine and 25 ml of dichloroethane with agitation
at room temperature. After the addition, the mixture
was heated at 60 to 62°C for 10 hours with agitation.
After cooling the reaction system with ice and the thus
deposited triethylamine hydrochloride was removed by
25 filtration, distilled water was added to the filtrate,
and organic layer was concentrated under reduced pressure,
after drying over anhydrous sodium sulfate.
Recrystallization of the residue from acetone gave
colourless crystals of the desired product, melting at
30 34 to 35°C in amount of 1.9g corresponding to the yield
of 46.4%.

Elementary analysis:

found : 62.70% C; 9.35% H and 12.73% N

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calcd. as $C_{17}H_{29}O_3N_3$:

63.13% C; 9.04% H and 12.99 N.

IR:

 $\nu_{\text{max}}^{\text{nujol}}$ 3500 - 3100 cm^{-1} (ν_{NH} and OH), 1755 cm^{-1} (ν ester)5 and 1660 and 1555 cm^{-1} (ν amide)Mass: m/e 323 (M^+).NMR (in CDCl_3) δ :0.85 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_8$)1.2 - 1.5 (15H, $\text{CH}_3(\text{CH}_2)_6(\text{CH}_2)_2$ and $\text{CH}_3\text{CH}_2\text{OCO}$)10 1.6 (2H, m, $\text{C}_7\text{H}_{15}\text{CH}_2\text{-CH}_3$)2.62 (2H, t, $J = 8$ Hz, $\text{C}_8\text{H}_{17}\text{CH}_2$)4.15 - 4.40 (4H, m, $\text{CONH-CH}_2\text{-CO}_2\text{-CH}_2\text{-CH}_3$)

6.52 (1H, s, H in the pyrazole ring)

15 7.6 (1H, br, NH in the ring, which disappear by treatment with D_2O)7.95 (1H, t-like, NH which disappear by the treatment with D_2O).EXAMPLE 12

20 Synthesis of 3-N-ethoxycarbonylmethylcarbamoyl-5-n-undecylpyrazole:

By the same procedures as in Example 11, 3.5 (0.013 mol) of 5-n-undecylpyrazole-3-carboxylic acid, was transformed to the corresponding amide of glycine. The crude product was recrystallized from acetone to provide the desired product as colourless crystals melting at 48 to 49°C in an amount of 2.0g corresponding to a yield of 43.8%.

Elementary analysis:

found : 64.37% C; 9.38% H and 11.25% N

30 calcd. as $C_{19}H_{33}O_3N_3$:

64.92% C; 9.46% H and 11.96% N.

IR:

$\nu_{\text{max}}^{\text{nujol}}$ 3500 - 3100 cm^{-1} (νNH and OH), 1750 cm^{-1}
(ester) 1660 and 1560 (ν amide)

Mass : m/e 351 (M^+).5 NMR (in CDCl_3) δ :0.89 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_{10}$)1.2 - 1.5 (19H, $\text{CH}_3(\text{CH}_2)_8(\text{CH}_2)_2$ and $\text{CH}_3\text{CH}_2\text{OCO}$)1.6 (2H, m, $\text{C}_9\text{H}_{19}\text{CH}_2\text{-CH}_2$)2.67 (2H, t, $J = 7$ Hz, $\text{C}_{10}\text{H}_{21} - \text{CH}_2$)10. 4.15 - 4.40 (4H, m, $\text{CONHCH}_2\text{CO}_2\text{CH}_2\text{CH}_3$)

6.62 (1H, s, H in the pyrazole ring)

8.20 (1H, t-like, NH which disappear by treatment
with D_2O)15 11.10 (1H, br. NH in the ring, disappearing by
treatment with D_2O)EXAMPLE 13

Synthesis of 3-N-ethoxycarbonylmethylcarbamoyl-
5-n-tridecylpyrazole:

By the same procedures as in Example 11, 2.9g
20 (0.01 mol) of 5-n-tridecylpyrazole-3-carboxylic acid,
was transformed to the corresponding amide of glycine.
The crude product was recrystallized from acetone to
provide the desired product as colourless needle-like
crystals melting at 54 to 55°C in an amount of 1.8g
25 corresponding to a yield of 47.4%.

Elementary analysis:

found: 66.30% C; 10.03% H and 10.81% N

calcd. as $\text{C}_{21}\text{H}_{37}\text{O}_3\text{N}_3$:

66.45 of C, 9.83% of H and 11.07% of N.

30 IR:

$\nu_{\text{max}}^{\text{nujol}}$ 3400 - 3100 cm^{-1} ($\nu\text{NH,OH}$), 1730 cm^{-1} (ν ester)
and 1640 and 1560 cm^{-1} (ν amide)

- 25 -

Mass: m/e 379 (M^+).NMR (in $CDCl_3$) δ :

- 0.89 (3H, t, $J = 6$ Hz, $CH_3(CH_2)_{12}$)
 1.2 - 1.5 (23H, $CH_3(CH_2)_{10}(CH_2)_2$ and CH_3CH_2OCO)
 5 1.6 (2H, m, $C_{11}H_{23}-CH_2-CH_2$)
 2.63 (2H, t, $J = 7$ Hz, $C_{12}H_{25}CH_2$)
 4.0 - 4.4 (4H, m, $CONH-CH_2-CO_2-CH_2CH_3$)
 6.55 (1H, s, H in the pyrazole ring)
 8.00 and 9.35 (1H each, br. NH X 2 which disappears
 10 by treatment with D_2O)

EXAMPLE 14

Synthesis of 3-hydroxymethyl-5-n-tridecylpyrazole:

- A solution of 11.0g (0.034 mol) of ethyl 5-n-tridecylpyrazole-3-carboxylate in 100 ml of anhydrous tetrahydrofuran, a suspension of 1.6g (0.042 mol) of lithium aluminum hydride in 150 ml of anhydrous tetrahydrofuran was added dropwise with stirring under cooling with ice. After stirring for 12 hours at room temperature, water-containing tetrahydrofuran was added to the reaction mixture. The deposited white precipitate was removed by filtration, and the filtrate was condensed to a solid and the residue recrystallized from ethyl ether to provide the desired product as colourless needle-like crystals melting at 64 to 66°C in an amount of 7.8g corresponding to a yield of 81.7%.
 Elementary analysis:

found: 72.85% C; 11.60% H and 10.01% N

calcd. as $C_{17}H_{32}ON_2$: 72.80% C; 11.50% H and 9.99% N.

30 IR:

$\nu_{\text{max}}^{\text{Nujol}}$ 3300 - 3100 cm^{-1} (ν NH and OH), and 1570

(ν pyrazole ring).

Mass : m/e 280 (M^+).

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NMR (in CDCl_3) δ :0.89 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_{12}$)1.2 - 1.5 (2H, br. s, $\text{CH}_3(\text{CH}_2)_{10}(\text{CH}_2)_2$)1.6 (2H, m, $\text{C}_{11}\text{H}_{23}-\text{CH}_2-\text{CH}_2$)5 2.56 (2H, t, $J = 8$ Hz, $\text{C}_{12}\text{H}_{25} - \text{CH}_2$)4.60 (2H, s, CH_2OH)

5.94 (1H, s, H in the pyrazole ring)

6.37 (2H, br. s, NH and OH disappearing by treatment with D_2O).10 EXAMPLE 15

Synthesis of 3-hydroxymethyl-5-n-heptylpyrazole:

In the same manner as in Example 14, 11.5g of ethyl 5-n-heptylpyrazole-3-carboxylate was reduced to the corresponding alcohol. The crude product was recrystallized from ethanol and n-hexane to provide the desired product as white plate-like crystals melting at 40 to 41°C in an amount of 7.5g corresponding to a yield of 76.9% of theoretical.

20 Elementary analysis:

found : 67.03% C; 10.18% H and 13.99% N

calcd. as $\text{C}_{11}\text{H}_{20}\text{ON}_2$:

67.30% C; 10.20% H and 14.27% N.

IR:

25 $\nu_{\text{max}}^{\text{nujol}}$ 3300 - 3100 cm^{-1} (ν NH and OH) and 1580
(ν pyrazole ring)

Mass: m/e 196 (M^+).NMR (in CDCl_3) δ :0.85 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_6$)30 1.2 - 1.5 (8H, br. s, $\text{CH}_3(\text{CH}_2)(\text{CH}_2)_2$)1.6 (2H, m, $\text{C}_5\text{H}_{11}-\text{CH}_2-\text{CH}_2$)2.50 (2H, t, $J = 8$ Hz, $\text{C}_6\text{H}_{13} - \text{CH}_2$)

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4.53 (2H, s, CH₂-OH)

5.83 (1H, s, H in the pyrazole ring)

8.48 (2H, br. s, NH and OH disappearing by
treatment with D₂O).

EXAMPLE 16

Synthesis of 3-hydroxymethyl-5-n-nonyl-pyrazole:

- In the same manner as in Example 14,
 5 14.5 g of -5-n-nonylpyrazole-3-carboxylate
 was reduced to the corresponding alcohol. The crude
 product was recrystallized from ethyl ether to provide
 the desired product as colourless needle-like
 crystals melting at 52 to 53°C in an amount of 10.6 g
 10 corresponding to a yield of 85.2%.

Elementary analysis:

found : 69.70% C; 10.68% H and 12.74% N

calcd. as $C_{13}H_{24}ON_2$:

69.60% C; 10.78% H and 12.49% N.

15 IR :

ν_{max} nujol 3300 - 3100 cm^{-1} (ν NH, OH) and 1580 cm^{-1}

(ν pyrazole group).

Mass: m/e 224 (M^+).

NMR (in $CDCl_3$) δ :

- 20 0.89 (3H, t, J = 6 Hz, $\underline{CH_3(CH_2)_8}$)
 1.2 - 1.5 (12H, br. s, $\underline{CH_3(CH_2)_6(CH_2)_2}$)
 1.6 (2H, m, $\underline{C_7H_{15}-CH_2-CH_2}$)
 2.54 (2H, t, J = 8 Hz, $\underline{C_8H_{17} - CH_2}$)
 4.58 (2H, s, $\underline{CH_2-OH}$)
 25 5.91 (1H, s, H in the pyrazole ring)
 8.00 (2H, br. s, NH and OH disappearing by
 treatment with D_2O)

EXAMPLE 17

Synthesis of 3-hydroxymethyl-5-n-undecyl-pyrazole:

In the same manner as in Example 14, 24.2 g.
 (0.034 mol) of ethyl 5-n-undecylpyrazole-3-carboxylate,
 was reduced to the corresponding alcohol. The crude

product was recrystallized from ethyl ether to provide 7.2 g of the desired product as colourless needle-like crystals melting at 56 to 58°C corresponding to a yield of 83.6%.

5 Elementary analysis:

found : 71.30% C; 11.46% H and 10.95% N

calcd. as $C_{15}H_{28}ON_2$:

71.33% C; 11.18% H and 11.10% N.

IR:

10 ν nujol max 3300 - 3100 cm^{-1} (ν NH and OH) and 1590 (ν pyrazole ring).

Mass : m/e 252 (M^+).

NMR (in $CDCl_3$) δ :

0.89 (3H, t, $J = 6$ Hz, $\underline{CH_3}(CH_2)_{10}$)
 15 1.2 - 1.5 (16H, br. s, $\underline{CH_3}(CH_2)_8(CH_2)_2$)
 1.6 (2H, m, $C_9H_{19}-\underline{CH_2}-CH_2$)
 2.55 (2H, t, $J = 8$ Hz, $C_{10}H_{21}-CH_2$)
 4.60 (2H, s, $\underline{CH_2}-OH$)
 5.92 (1H, s, H in the pyrazole ring)
 20 8.54 (1H, br. s, NH and OH disappearing by treatment with D_2O)

EXAMPLE 18

Synthesis of 1-methyl-5-n-nonylpyrazole-3-carboxylic acid:

25 20.0 g (0.069 mol) of sodium-1-ethoxycarbonyl-3-oxo-1-dodecenolate and 10.1 g (0.053 mol) of methylhydrazine sulfate were dissolved in 45 ml of distilled water, and then 14 ml of aqueous 33% solution of sodium hydroxide was added dropwise. Then, the mixture was
 30 heated for one hour at 80°C with agitation, and after cooling, it was made acidic with 6N sulfuric acid solution and extracted with chloroform. The chloroform

layer was washed with a saturated aqueous solution of sodium chloride, dried over anhydrous sodium sulfate and concentrated under a reduced pressure. By recrystallizing the residue from a mixture of acetone and isopropyl ether, 1-methyl-5-n-nonylpyrazole-3-carboxylic acid was obtained as colourless needle-like crystals melting at 87°C in an amount of 11.3 g corresponding to a yield of 64.7%.

Elementary analysis:

found : 66.90% C; 9.61% H and 11.24% N
calcd. as $C_{14}H_{24}O_2N_2$:
66.63% C; 9.59% H and 11.10% N.

IR :

ν_{max} nujol 3000 - 2500 cm^{-1} (ν CO_2H) and 1680 cm^{-1} (ν C = O).

Mass : m/e 252 (M^+).

NMR (in d_6 -DMSO) δ :

0.89 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_8$)
1.2 - 1.6 (12H, br. s, $\text{CH}_3(\text{CH}_2)_6(\text{CH}_2)_2$)
1.7 (2H, m, $\text{CH}_3(\text{CH}_2)_6\text{-CH}_2\text{-CH}_2$)
2.62 (2H, t, $J = 8$ Hz, $\text{CH}_3(\text{CH}_2)_7\text{-CH}_2$)
3.83 (3H, s, N-CH_3)
6.50 (1H, s, H in the pyrazole ring)
8.4 (1H, br., CO_2H , which disappear by treatment with D_2O)

EXAMPLE 19

Synthesis of 1-methyl-5-n-heptylpyrazole-3-carboxylic acid:

In the same manner as in Example 18, 26.4 (0.1 mol) of sodium 1-ethoxycarbonyl-3-oxo-1-decenolate was cyclized to the corresponding N-methylpyrazole derivative. The crude product was recrystallized from ethanol to provide 1-methyl-5-n-heptylpyrazole-3-carboxylic

acid as white powdery crystals melting at 80°C in an amount of 11.7 g corresponding to a yield of 56.5%.

Elementary analysis:

found: 64.50% C; 9.12% H and 12.50% N.

5 calcd. as $C_{12}H_{20}O_2N_2$:

64.25% of C, 8.88% of H and 12.49% of N.

IR :

ν_{max} nujol 3000 -2500 cm^{-1} (ν CO_2H) and 1680 cm^{-1} (ν $\text{C}=\text{O}$).

Mass : m/e 224 (M^+)

10 NMR : (in d_6 -DMSO) δ :

0.89 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_6$)

1.2 - 1.6 (8H, br. s, $\text{CH}_3(\text{CH}_2)_4(\text{CH}_2)_2$)

1.7 (2H, m, $\text{CH}_3(\text{CH}_2)_4-\text{CH}_2-\text{CH}_2$)

2.62 (2H, t, $J = 8$ Hz, $\text{CH}_3(\text{CH}_2)_5 - \text{CH}_2$)

15 3.80 (3H, s, $\text{N}-\text{CH}_3$)

6.50 (1H, s, H in the pyrazole ring)

8.4 (1H, br., CO_2H which disappears by treatment with D_2O)

EXAMPLE 20

20 Synthesis of 1-methyl-5-n-undecylpyrazole-3-carboxylic acid:

In the same manner as in Example 18, 20.0 g of sodium 1-ethoxycarbonyl-3-oxo-1-tetradecenolate was cyclized to the corresponding N-methylpyrazole derivative.

25 The crude product was recrystallized from a mixture of acetone and isopropyl ether to provide 1-methyl-5-n-undecylpyrazole-3-carboxylic acid as colourless needle-like crystals melting at 79°C in an amount of 12.6 g corresponding to a yield of 75.0%.

30 Elementary analysis:

found : 68.79% C, 10.08% H and 10.15% N

calcd. as $C_{16}H_{28}O_2N_2$:

68.53% C; 10.07% H and 9.99% N.

IR :

$\nu_{\text{max}}^{\text{nujol}}$ 3000 - 2500 cm^{-1} (ν CO_2H) and 1680 cm^{-1} (ν C = O).

Mass : m/e 280 (M^+).

NMR (in d_6 -DMSO) δ :

- 5 0.87 (3H, t, J = 6 Hz, $\text{CH}_3(\text{CH}_2)_{10}$)
 1.2 - 1.5 (16H, br. s, $\text{CH}_3(\text{CH}_2)_8(\text{CH}_2)_2$)
 1.6 (2H, m, $\text{C}_9\text{H}_{19}\text{-CH}_2\text{-CH}_2$)
 2.62 (2H, t, J = 8 Hz, $\text{C}_{10}\text{H}_{21}\text{-CH}_2$)
 2.80 (3H, s, N- CH_3)
 10 6.47 (1H, s, H in the pyrazole ring)
 11.8 (1H, br. CO_2H which disappears by treatment
 with D_2O)

EXAMPLE 21

- 15 Synthesis of 1-methyl-5-n-tridecylpyrazole-3-carboxylic acid:

- In the same manner as in Example 18, 20.0 g of sodium 1-ethoxycarbonyl-oxo-1-hexadecenolate was cyclized to the corresponding N-methylpyrazole derivative. The crude product was recrystallized from a mixture of
 20 acetone and isopropyl ether to provide 1-methyl-5-n-tridecylpyrazole-3-carboxylic acid as colourless needle-like crystals melting at 82 to 83°C in an amount of 10.1 g corresponding to a yield of 57.2%.

Elementary analysis:

- 25 found : 70.26% C; 10.38% H and 8.88% N
 calcd. as $\text{C}_{18}\text{H}_{32}\text{O}_2\text{N}_2$:
 70.09% C; 10.46% H and 9.08% N.

IR :

$\nu_{\text{max}}^{\text{nujol}}$ 3000 - 2500 cm^{-1} (ν CO_2H) and 1680 cm^{-1} (ν C = O)

- 30 Mass : m/e 308 (M^+).

NMR (in d_6 -DMSO) δ :

0.87 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_{12}$)

1.2 - 1.5 (20H, br. s, $\text{CH}_3(\text{CH}_2)_{10}(\text{CH}_2)_2$)

1.6 (2H, m, $\text{C}_{11}\text{H}_{23}-\text{CH}_2-\text{CH}_2$)

2.61 (2H, t, $J = 8$ Hz, $\text{C}_{12}\text{H}_{25}-\text{CH}_2$)

5 3.80 (3H, s, $\text{N}-\text{CH}_3$)

6.47 (1H, s, H in the pyrazole ring)

10.8 (1H, br., CO_2H which disappears by treatment with D_2O)

EXAMPLE 22

10 Synthesis of 1-phenyl-5-n-nonylpyrazole-3-carboxylic acid:

10.0 g (0.034 mol) of sodium 1-ethoxycarbonyl-3-oxo-1-dodecenolate and 8.2 g (0.026 mol) of phenylhydrazine sulfate were dissolved in 40 ml of methanol, and 20 ml of saturated methanolic solution of sodium hydroxide were added dropwise. After the addition, the mixture was gently heated for 2 hours under reflux and after making it acidic with concentrated hydrochloric acid and adding distilled water, methanol was removed under a reduced pressure. The residue was extracted with chloroform, and the chloroform layer was washed with a saturated aqueous solution of sodium chloride and dried over anhydrous sodium sulfate and concentrated. The residue was recrystallized from ethanol to provide 5.0 g of the desired product as colourless needle-like crystals melting at 87 to 88°C corresponding to a yield of 61.7%.

Elementary analysis:

found : 72.47% C; 8.05% H and 8.84% N

calcd. as $\text{C}_{19}\text{H}_{26}\text{O}_2\text{N}_2$:

30 72.58% C; 8.34% H and 8.91% N.

IR :

ν_{max} nujol 3000 - 2500 cm^{-1} (ν CO_2H), 1700 cm^{-1} (ν C = O) and 1600 cm^{-1} (ν benzene ring)

Mass : m/e 314 (M^+).

NMR (in d_6 -DMSO) δ :

- 0.85 (3H, t, $J = 6$ Hz, $CH_3(CH_2)_8$)
 1.2 - 1.5 (12H, br. s, $CH_3(CH_2)_6(CH_2)_2$)
 5 1.6 (2H, m, $C_7H_{15}-CH_2-CH_2$)
 2.52 (2H, t, $J = 8$ Hz, $C_2H_{17}-CH_2$)
 6.67 (1H, s, H in the pyrazole ring)
 7.51 (5H, m, 5 X H in the benzene ring)
 11.0 (1H, br., CO_2H , disappearing by treatment with
 10 D_2O)

EXAMPLE 23

Synthesis of 1-phenyl-5-n-heptylpyrazole-3-carboxylic acid:

- In the same manner as in Example 18, 9.0 g
 15 (0.034 mol) of sodium 1-ethoxycarbonyl-3-oxo-1-decenolate
 was reacted with 8.2 g (0.026 mol) of phenylhydrazine
 sulfate to give the corresponding 1-phenylpyrazole
 derivative as a crude oil. After treatment with
 activated carbon, the residue was distilled under a
 20 reduced pressure to provide 5.5 g of a colourless oil
 with a boiling point of 97 to 98°C/0.28 mmHg at a yield
 of 56.7%.

Elementary analysis:

- found: 71.40% C; 7.47% H and 9.95% N
 25 calcd. as $C_{17}H_{22}O_2N_2$:
 71.30% C; 7.74% H and 9.78% N.

IR :

ν_{max} nujol 3000 - 2500 cm^{-1} (ν CO_2H), 1700 cm^{-1} (ν C = O)
 and 1600 cm^{-1} (ν benzene ring).

- 30 Mass: m/e 286 (M^+).

NMR (in $CDCl_3$) δ :

- 35 -

- 0.89 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_6$)
 1.2 - 1.5 (8H, br. $\text{CH}_3(\text{CH}_2)_4-(\text{CH}_2)_2$)
 1.6 (2H, m, $\text{C}_5\text{H}_{11}-\text{CH}_2-\text{CH}_2$)
 2.60 (2H, t, $J = 8$ Hz, $\text{C}_6\text{H}_{13}-\text{CH}_2$)
 5 6.72 (1H, s, H in the pyrazole ring)
 7.40 (5H, br. s, 5 X H in the benzene ring)
 10.8 (1H, br., CO_2H disappearing by treatment with D_2O).

EXAMPLE 24

- 10 Synthesis of 1-phenyl-5-n-undecylpyrazole-3-carboxylic acid:

- In the same manner as in Example 18, 11.0 g (0.034 mol) of sodium 1-ethoxycarbonyl-3-oxo-1-tetradecenolate was reacted with 8.2 g (0.026 mol) of
 15 phenylhydrazine sulfate to give the corresponding 1-phenylpyrazole derivative. The crude product was recrystallized from ethanol to provide 8.1 g of colourless needle-like crystals melting at 53 to 55°C corresponding to a yield of 69.7%.

- 20 Elementary analysis:

 found: 73.70% C; 8.91% H and 8.40% N

 calcd. as $\text{C}_{21}\text{H}_{30}\text{O}_2\text{N}_2$:

 73.64% C; 8.83% H and 8.18% N.

IR:

- 25 ν_{max} nujol 3000 - 2500 cm^{-1} (ν CO_2H), 1700 cm^{-1} (ν C = O)
 and 1600 cm^{-1} (ν benzene ring).

Mass: m/e 342 (M^+).

NMR (in d_6 -DMSO) δ :

- 36 -

- 0.86 (3H, t, $J = 6$ Hz, $\text{CH}_3(\text{CH}_2)_{10}$)
 1.2 - 1.5 (16H, br. s, $\text{CH}_3(\text{CH}_2)_8(\text{CH}_2)_2$)
 1.6 (2H, m, $\text{C}_9\text{H}_{19}-\text{CH}_2-\text{CH}_2$)
 2.65 (2H, t, $J = 8$ Hz, $\text{C}_{10}\text{H}_{21} - \text{CH}_2$)
 5 6.70 (1H, s, H in the pyrazole ring)
 7.52 (5H, br. s, 5 X H in the benzene ring)
 12.3 (1H, br., CO_2H disappearing by treatment with D_2O)

EXAMPLE 25

- 10 Synthesis of 1-phenyl-5-n-tridecylpyrazole -3-carboxylic acid:

In the same manner as in Example 18, 9.0 g (0.026 mol) of sodium 1-ethoxycarbonyl-3-oxo-1-hexadecenolate was reacted with 6.3 g (0.020 mol) of phenylhydrazine sulfate to give the corresponding 1-phenylpyrazole derivative. The crude product was recrystallized from ethanol to provide colourless needle-like crystals melting at 89 to 90°C in an amount of 4.4 g corresponding to a yield of 59.8%.

- 20 Elementary analysis:

found: 74.08% C; 9.52% H and 7.59% N

calcd. as $\text{C}_{23}\text{H}_{34}\text{O}_2\text{N}_2$:

74.55% C; 9.25% H and 7.56% N.

IR :

- 25 $\nu_{\text{max}}^{\text{nujol}}$ 3000 - 2500 cm^{-1} ($\nu \text{ CO}_2\text{H}$), 1700 cm^{-1} ($\nu \text{ C} = \text{O}$)
 and 1600 cm^{-1} (ν benzene ring)

Mass: m/e 370 (M^+).

NMR (in CDCl_3) δ :

- 0.87 (3H, t, J = 6 Hz, $\text{CH}_3(\text{CH}_2)_{12}$)
 1.2 - 1.5 (20H, br. s, $\text{CH}_3(\text{CH}_2)_{10}(\text{CH}_2)_2$)
 1.7 (2H, m, $\text{C}_{11}\text{H}_{23}-\text{CH}_2\text{CH}_2$)
 2.60 (2H, t, J = 8 Hz, $\text{C}_{12}\text{H}_{25} - \text{CH}_2$)
 5 6.58 (1H, s, H in the pyrazole ring)
 7.4 - 7.8 (5H, m, 5 X H in the benzene ring)
 12.0 (1H, br., CO_2H disappearing by treatment with D_2O)

Figures 1 to 25 of the accompanying drawings
 10 show the infrared absorption spectra of the pyrazole
 derivatives prepared in accordance with Examples 1 to
 25, the number of each Figure corresponding to the number
 of the appropriate Example.

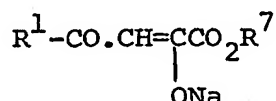
EXAMPLE 26

15 200 G of 5-n-tridecylpyrazole-3-carboxylic
 acid, 50 g of lactose, 20 g of potato starch, 15 g of
 CMC and 10 g of methylcellulose were mixed uniformly,
 the mixture was shaped into particles by introducing the
 mixture together with an aqueous 50% ethanolic solution
 20 into a tumbling forming machine, and the thus obtained
 particles were dried using a fluidizing dryer. After
 drying, the particles were sifted by screening machine
 provided with a sieve having a sieve opening of 500
 microns (32 mesh Tyler standard). The particles passing
 25 through the sieve were mixed with 3 g of talc and 2 g
 of magnesium stearate and the mixture was pressed in a
 rotary tabletting machine into tablets each 9 mm in
 diameter and 300 mg in weight.

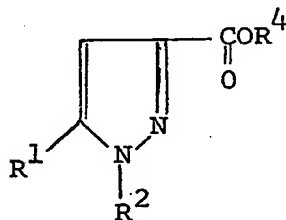
EXAMPLE 27

Particles were prepared by the same procedure as in Example 26, but using ethyl 5-n-tridecylpyrazole-3-carboxylate instead of the acid itself used in Example 26, and the particles were capsulated in No. 1 hard capsules by using a capsulating machine at a rate of 300 mg/capsule.

The pyrazole derivatives of general formula (I) can in general be prepared by reacting a sodium enolate of the formula



wherein R^7 represents a lower alkyl group with hydrazine hydrate or a hydrazine sulfate of the formula $\text{R}^2\text{NH}\cdot\text{NH}_2\cdot\text{H}_2\text{SO}_4$ to form a 5-alkylpyrazole-3-carboxylic acid or an alkyl ester thereof of the formula



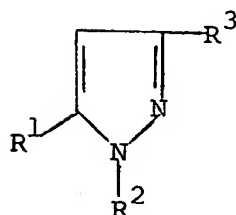
wherein R^4 is hydrogen or a lower alkyl group, and if desired, when R^4 is lower alkyl converting the alkyl ester to the corresponding acid wherein R^4 is hydrogen by hydrolysis or to a pyrazole derivative in which R^3 is $-\text{CH}_2\text{OH}$ by reduction, or when R^4 is hydrogen converting the carboxylic acid to a pyrazole derivative in which R^3 is $-\text{C}=\text{O}$ by forming the

$$\begin{array}{c} | \\ \text{NH-R}^5 \end{array}$$

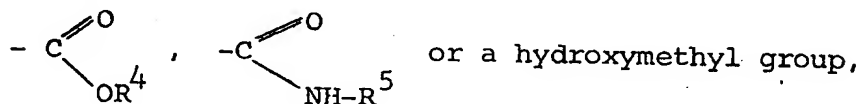
acid chloride from the carboxylic acid and reacting the acid chloride with an amine derivative of the formula NH_2R^5 or a hydrochloride thereof or to the alkyl ester wherein R^4 is lower alkyl by esterification.

CLAIMS

1. A pyrazole derivative of the general formula:

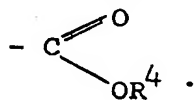


wherein R^1 represents an alkyl group of 7 to 17 carbon atoms, R^2 represents a hydrogen atom, a lower alkyl group or a phenyl group and R^3 represents

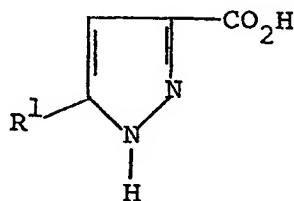


wherein R^4 represents a hydrogen atom or a lower alkyl group and R^5 represents $-\text{CH}_2\text{CH}_2\text{OH}$ or $-\text{CH}_2-\underset{\text{R}^6}{\text{C}}=\text{O}$,

wherein R^6 represents a hydroxyl group or a lower alkoxy group, with the proviso that when R^1 represents an alkyl group of 7 to 11 carbon atoms and R^2 represents a hydrogen atom, R^3 does not represent



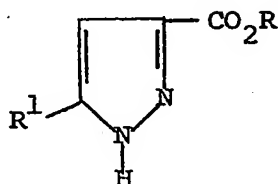
2. A pyrazole derivative according to claim 1 which is a 5-alkylpyrazole-3-carboxylic acid of the formula:



- 40 -

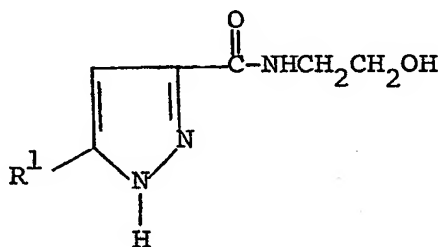
wherein R^1 represents an alkyl group of 13 to 17 carbon atoms.

3. A pyrazole derivative according to claim 1 which is a 5-alkylpyrazole-3-carboxylic acid ester of the formula:



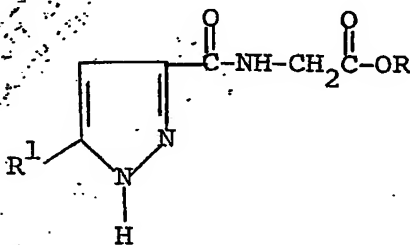
wherein R represents a lower alkyl group and R^1 represents an alkyl group of 13 to 17 carbon atoms.

4. A pyrazole derivative according to claim 1 which is a 3-N-2'-hydroxyethylcarbamoyl-pyrazole of the formula:



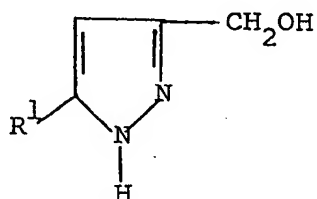
wherein R^1 represents an alkyl group of 9 to 17 carbon atoms.

5. A pyrazole derivative according to claim 1 which is a 3-N-alkoxycarbonylmethylcarbamoyl-pyrazole of the formula:



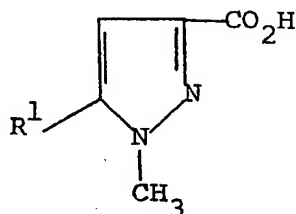
wherein R represents a lower alkyl group and R^1 represents an alkyl group of 9 to 13 carbon atoms.

6. A pyrazole derivative according to claim 1 which is a 3-hydroxymethylpyrazole of the formula:



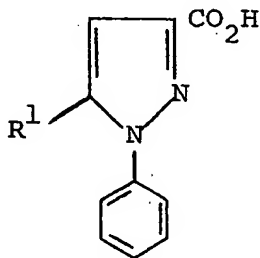
wherein R^1 represents an alkyl group of 7 to 13 carbon atoms.

7. A pyrazole derivative according to claim 1 which is a 1-methyl-5-alkylpyrazole-3-carboxylic acid of the formula:



wherein R^1 represents an alkyl group of 7 to 13 carbon atoms.

8. A pyrazole derivative according to claim 1 which is a 1-phenyl-5-alkylpyrazole-3-carboxylic acid of the formula:



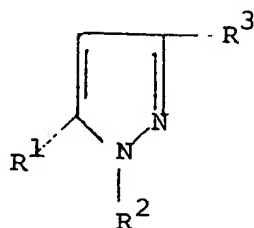
- 42 -

wherein R¹ represents an alkyl group of 7 to 13 carbon atoms.

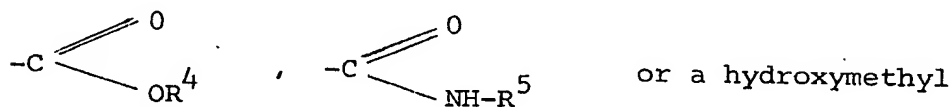
9. A pharmaceutical composition comprising, as active ingredient, a pyrazole derivative as claimed in any one of claims 1 to 8, together with a pharmaceutically acceptable carrier.

CLAIMS FOR AUSTRIA

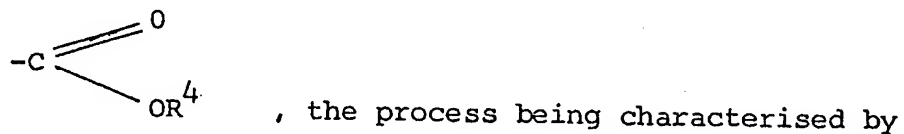
1. A process for preparing pyrazole derivative of the general formula:



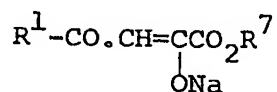
wherein R^1 represents an alkyl group of 7 to 17 carbon atoms, R^2 represents a hydrogen atom, a lower alkyl group or a phenyl group and R^3 represents



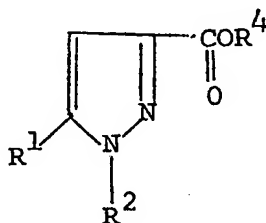
group, wherein R^4 represents a hydrogen atom or a lower alkyl group and R^5 represents $-\text{CH}_2\text{CH}_2\text{OH}$ or $-\text{CH}_2-\underset{\text{R}^6}{\text{C}}=\text{O}$, wherein R^6 represents a hydroxyl group or a lower alkoxy group, with the proviso that when R^1 represents an alkyl group of 7 to 11 carbon atoms and R^2 represents a hydrogen atom, R^3 does not represent



reacting a sodium enolate of the formula



wherein R^7 represents a lower alkyl group with hydrazine hydrate or a hydrazine sulfate of the formula $R^2NH.NH_2.H_2SO_4$ to form a 5-alkylpyrazole-3-carboxylic acid or an alkyl ester thereof of the formula



wherein R^4 is hydrogen or a lower alkyl group, and, if desired, when R^4 is lower alkyl converting the alkyl ester to the corresponding acid wherein R^4 is hydrogen by hydrolysis or to a pyrazole derivative in which R^3 is $-CH_2OH$ by reduction, or when R^4 is hydrogen converting the carboxylic acid to a pyrazole derivative in which R^3 is $-C(=O)NH-R^5$ by forming the acid chloride from the

carboxylic acid and reacting the acid chloride with an amine derivative of the formula NH_2R^5 or a hydrochloride thereof or to the alkyl ester wherein R^4 is lower alkyl by esterification.

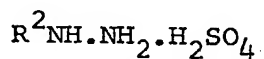
2. A process according to claim 1 characterised in that an alkyl ester of a 5-alkylpyrazole-3-carboxylic acid is prepared by reacting the sodium enolate with hydrazine hydrate in a mineral acid, and if desired the carboxylic acid is prepared by hydrolysing the alkyl ester.

3. A process according to claim 1 characterised in that a 5-alkylpyrazole-3-carboxylic acid is prepared by reacting the sodium enolate with hydrazine sulfate in an aqueous solution of sodium hydroxide.

4. A process according to claim 3 characterised in that a 5-alkylpyrazol-3-carboxamide is formed by reacting the 5-alkylpyrazole-3-carboxylic acid with thionyl chloride to provide the carboxylic acid chloride and reacting the carboxylic acid chloride with the amine derivative of formula NH_2R^5 or hydrochloride thereof in dichloroethane in the presence of triethylamine.

5. A process according to claim 1 characterised in that a 3-hydroxymethyl-5-alkylpyrazole is prepared by reducing the alkyl ester of a 5-alkylpyrazole-3-carboxylic acid with lithium aluminium hydride in anhydrous tetrahydrofuran.

6. A process according to claim 1 characterised in that a 1-alkyl or phenyl-5-alkylpyrazole-3-carboxylic acid is produced by dissolving the sodium enolate in water or methanol together with a hydrazine sulfate of the formula



wherein R^2 is lower alkyl or phenyl, adding sodium hydroxide to the resulting solution and heating the mixture.

FIG. 1

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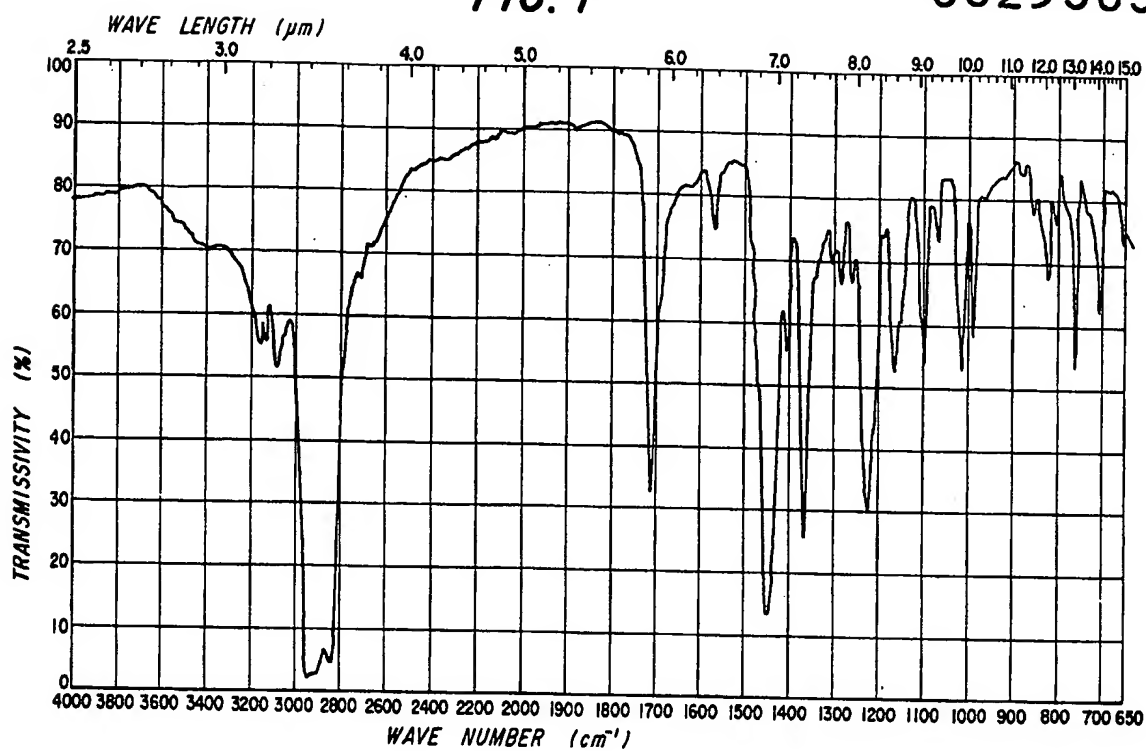
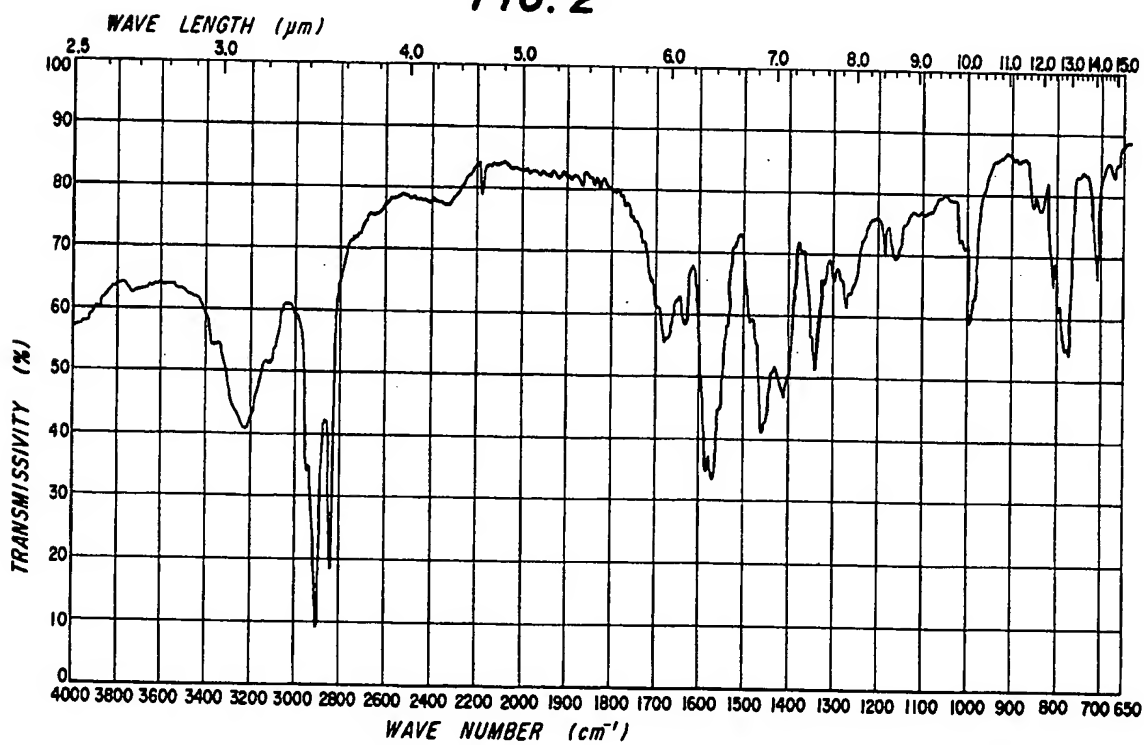


FIG. 2



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VIC-3

FIG. 3

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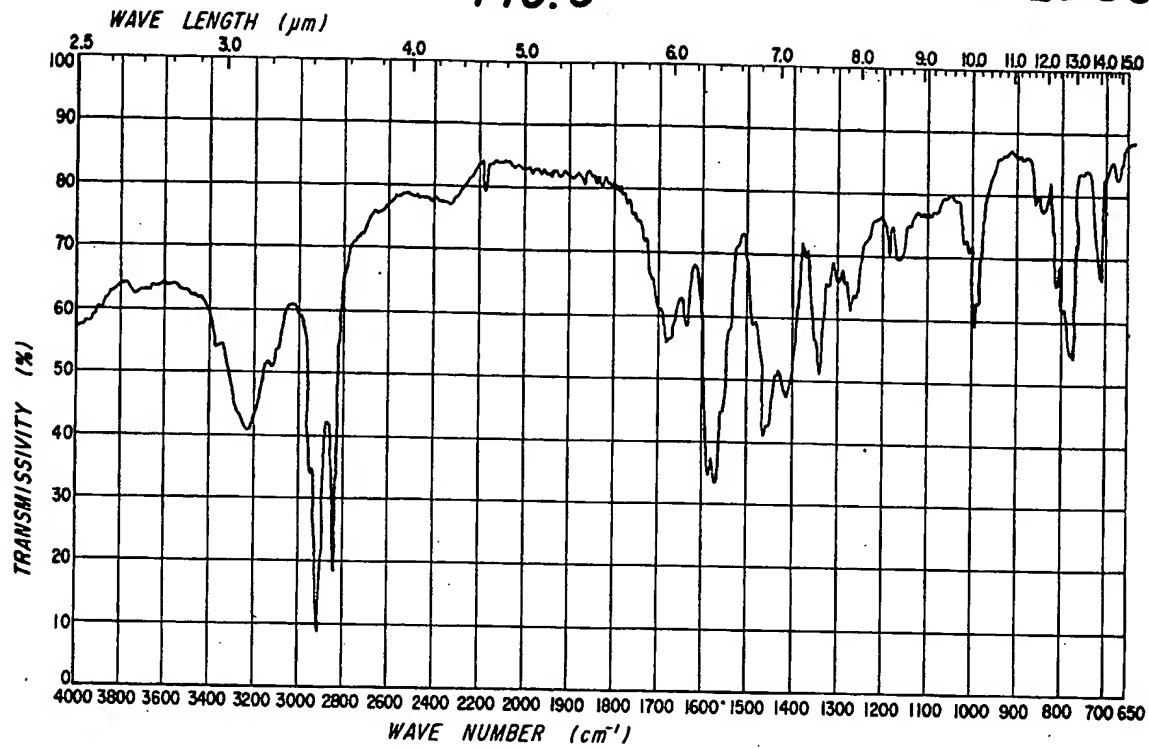
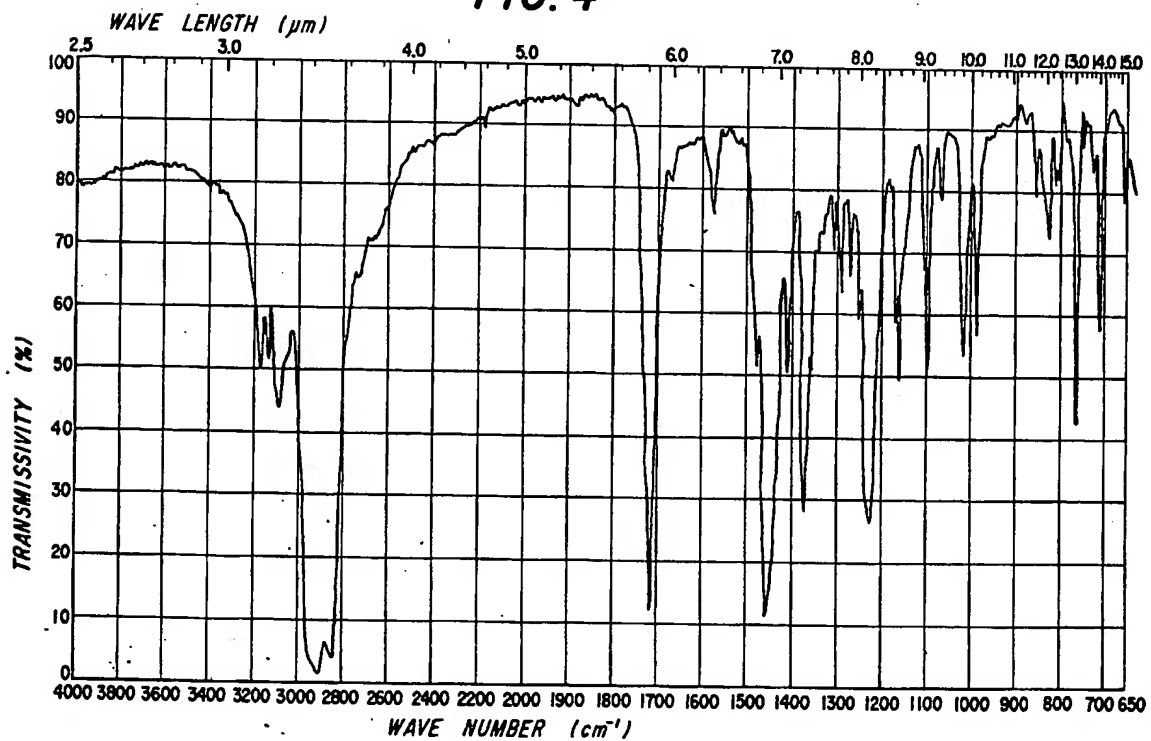


FIG. 4



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MCC-2

FIG. 5

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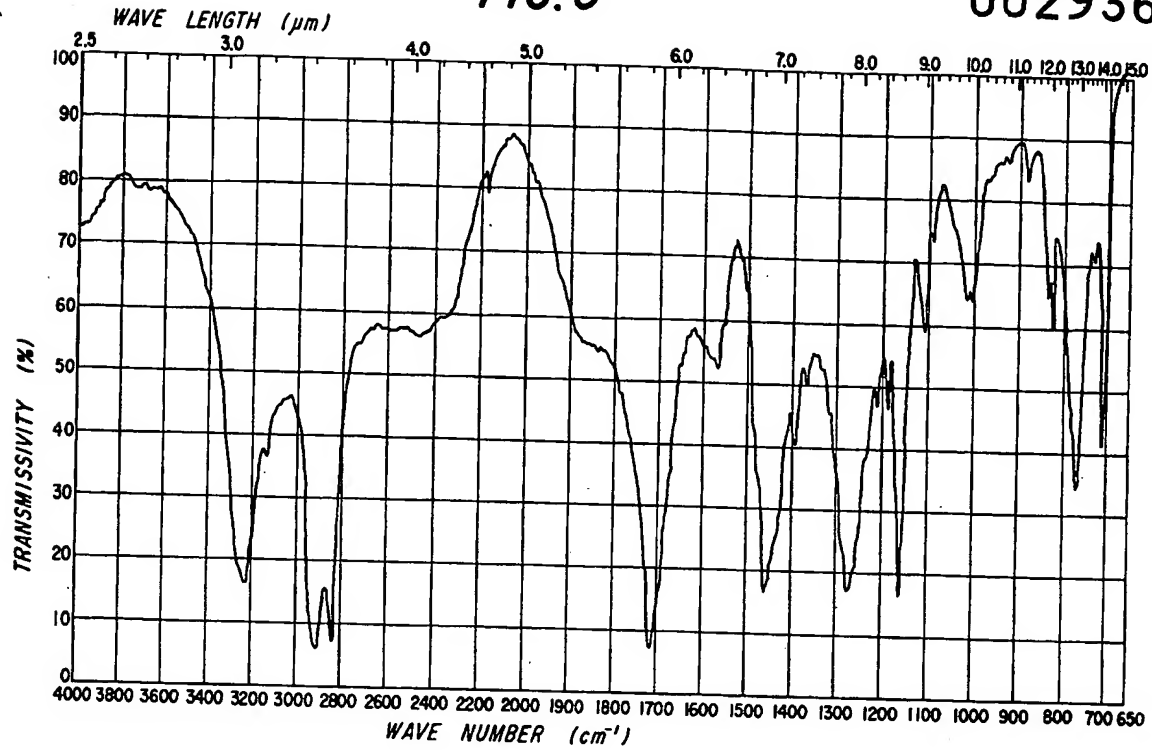
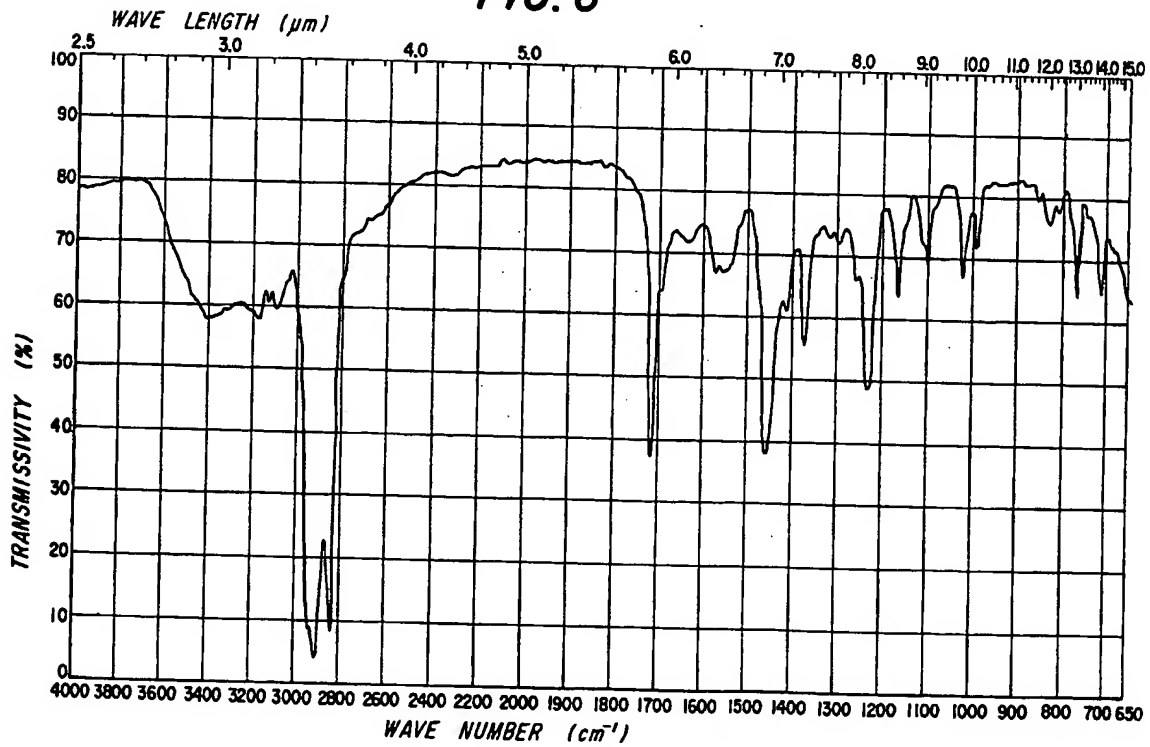


FIG. 6



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FIG. 7

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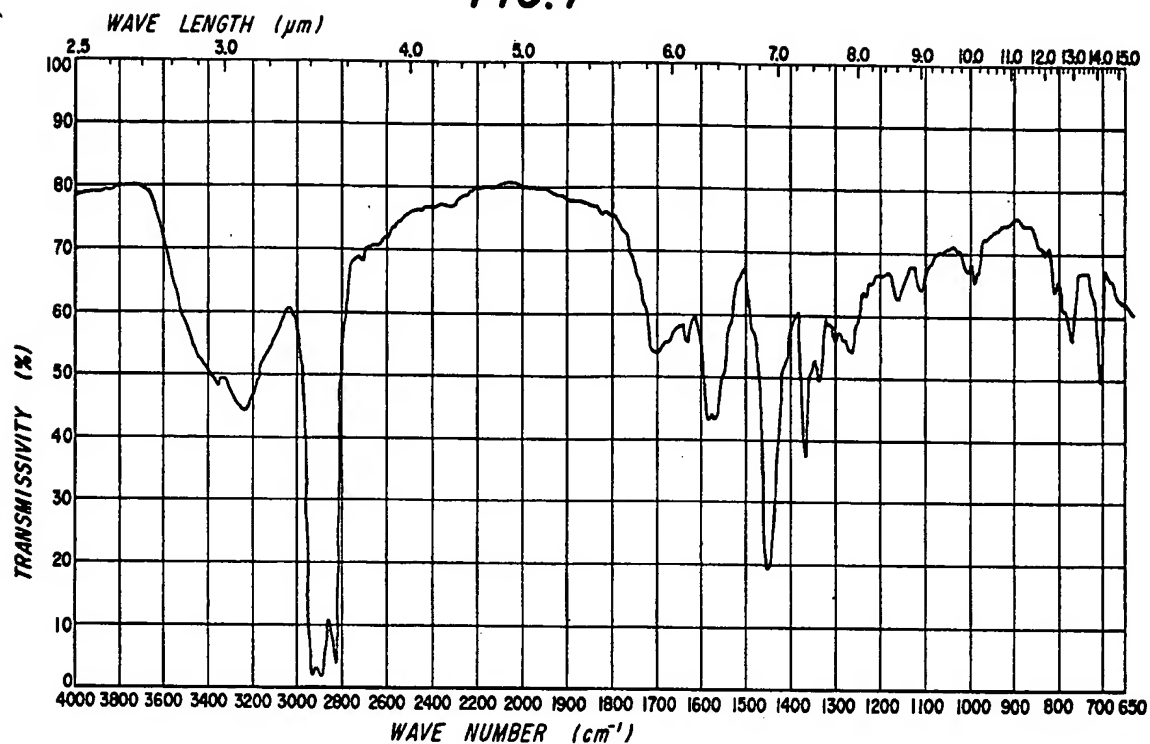
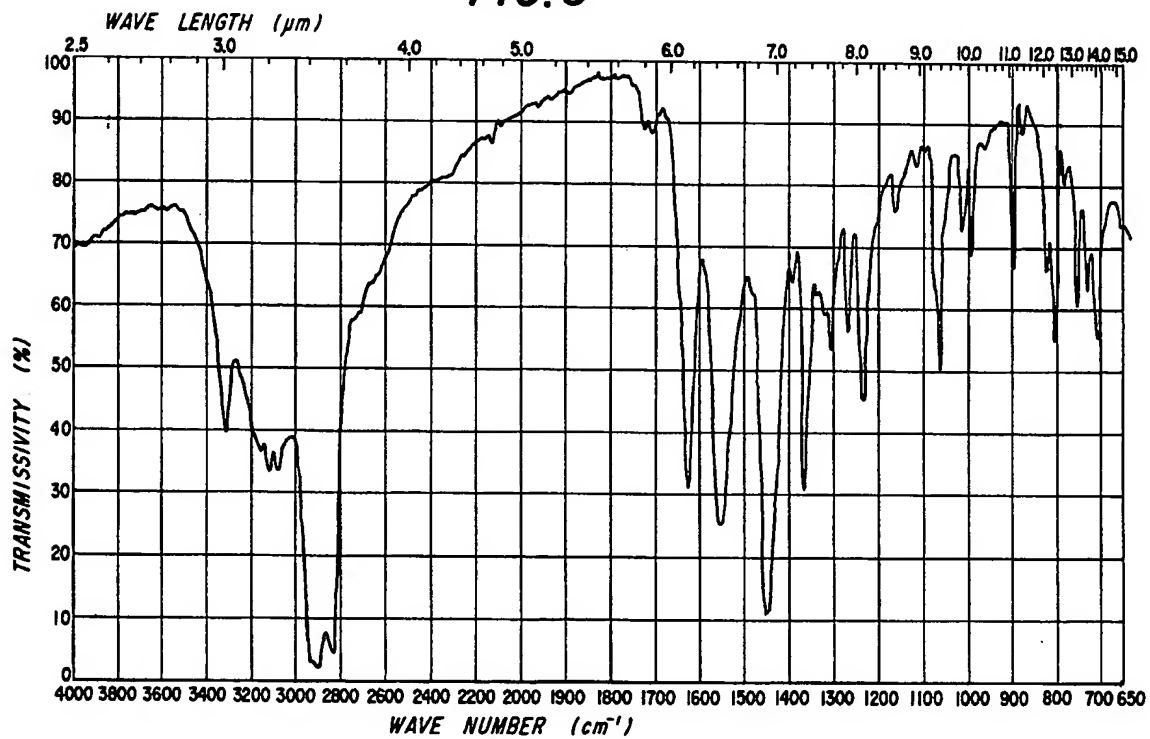


FIG. 8



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FIG. 9

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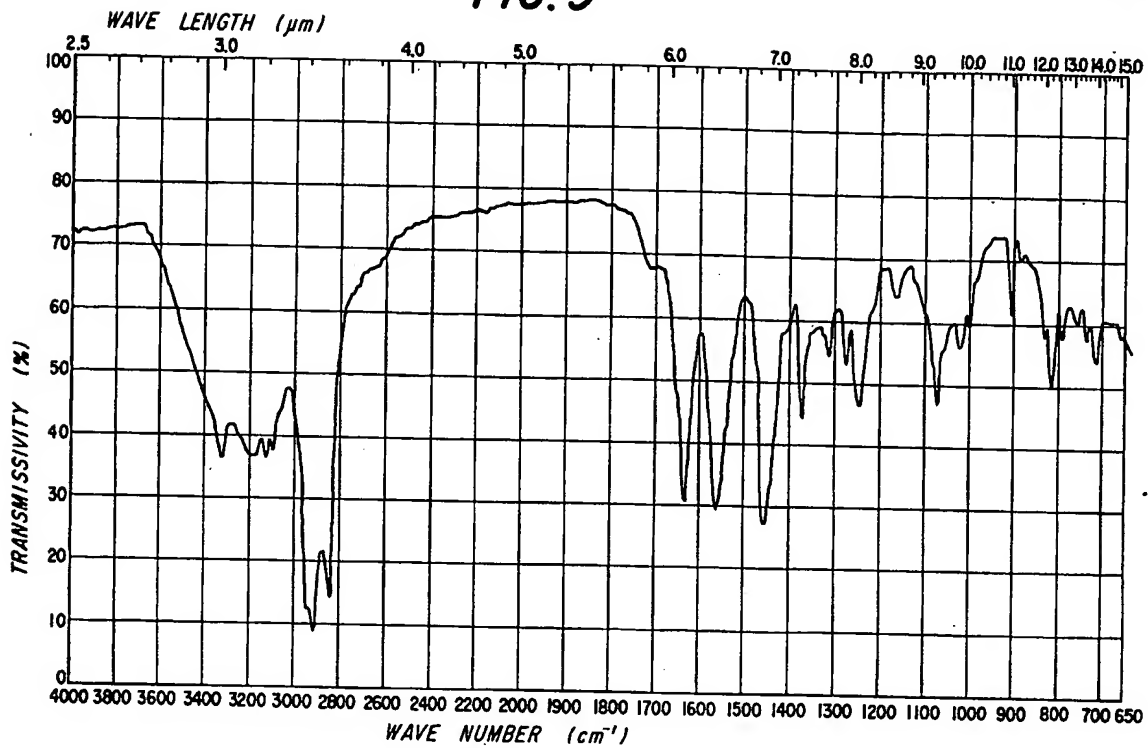
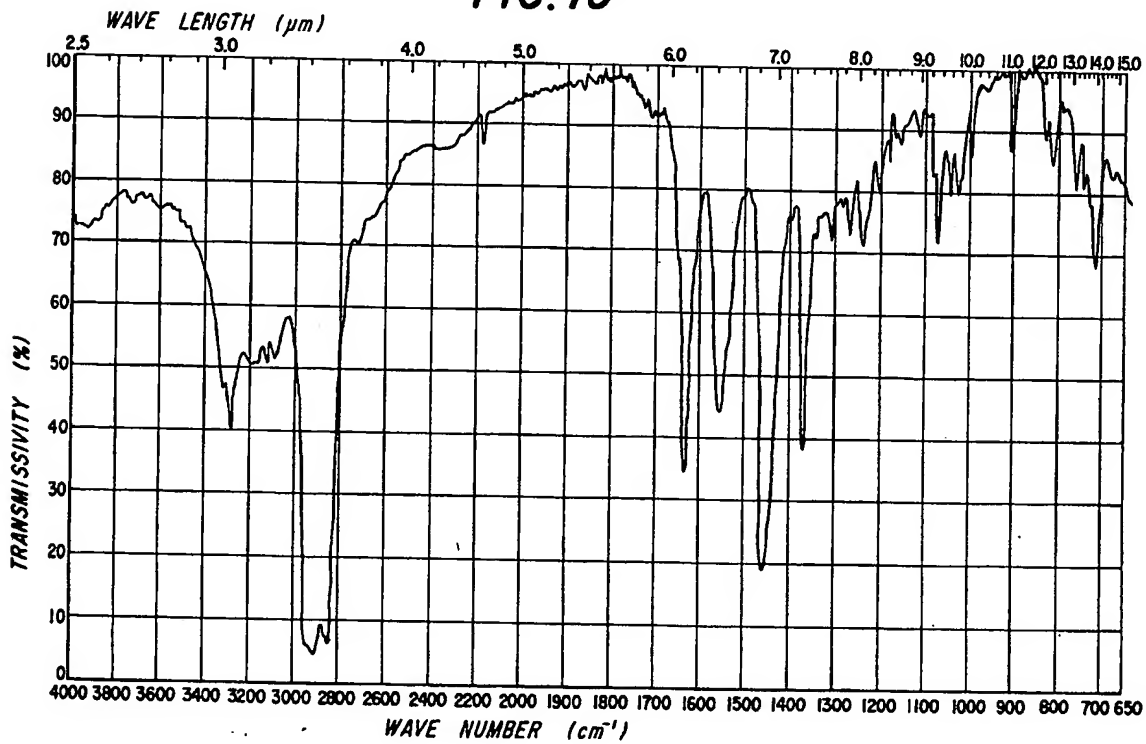


FIG. 10



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FIG. 11

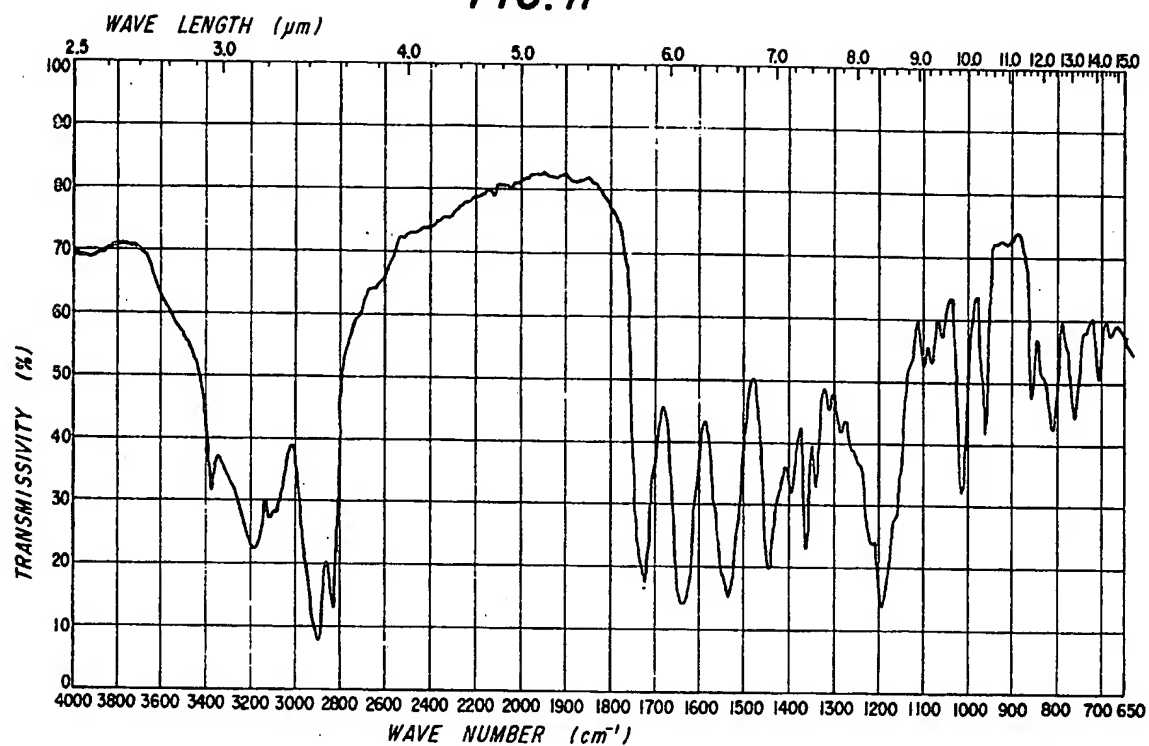
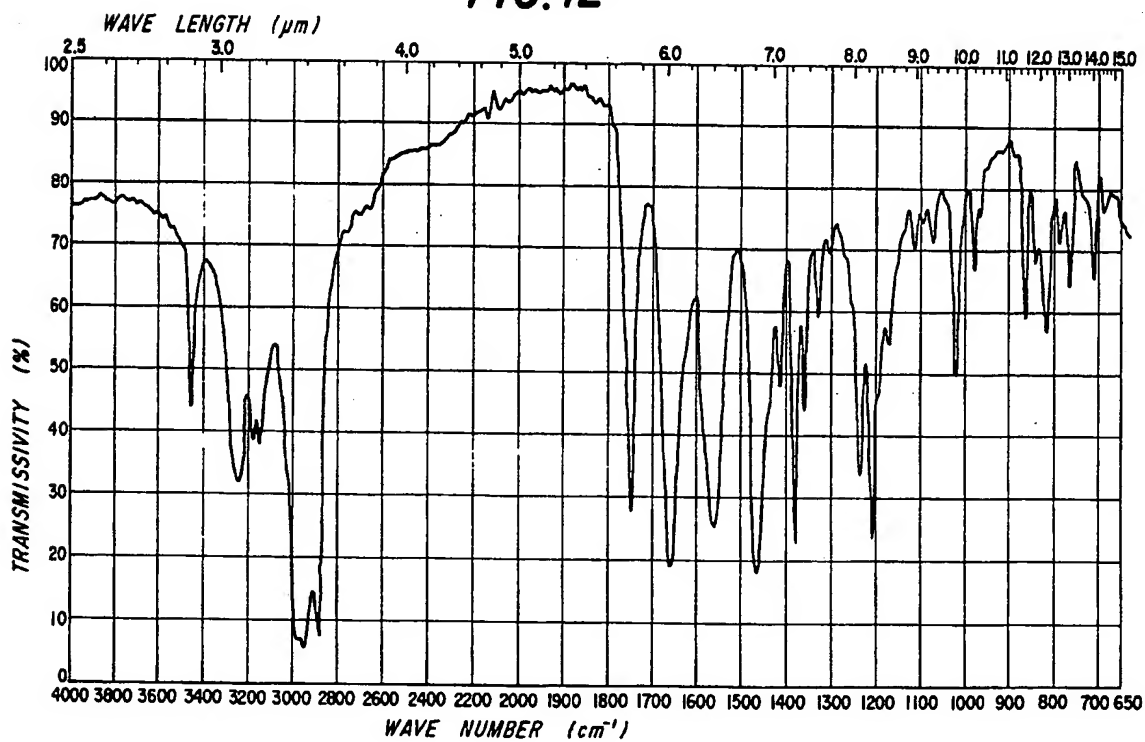


FIG. 12



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FIG. 13

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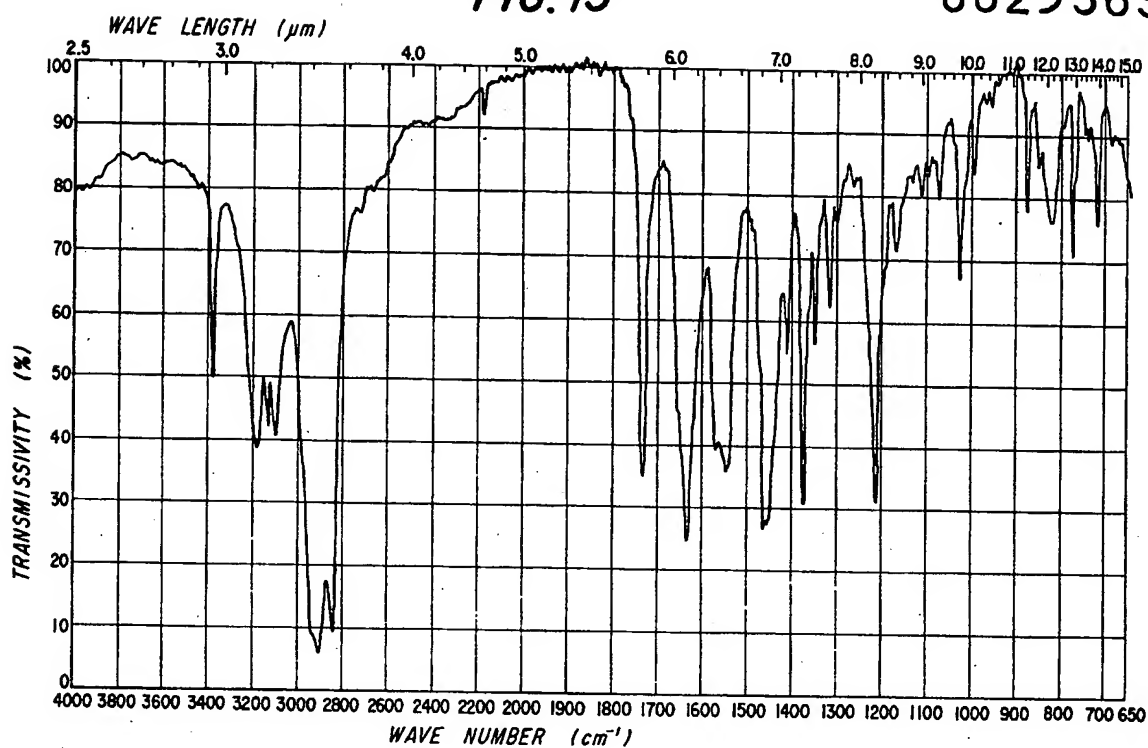
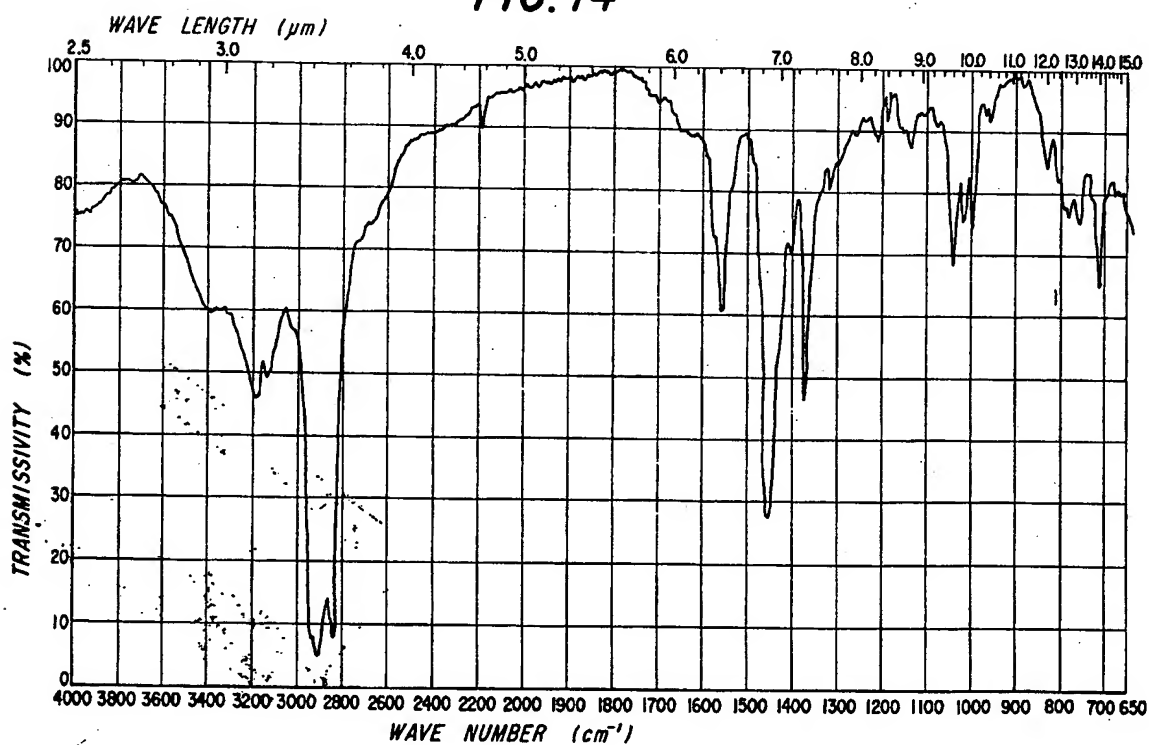


FIG. 14



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FIG. 15

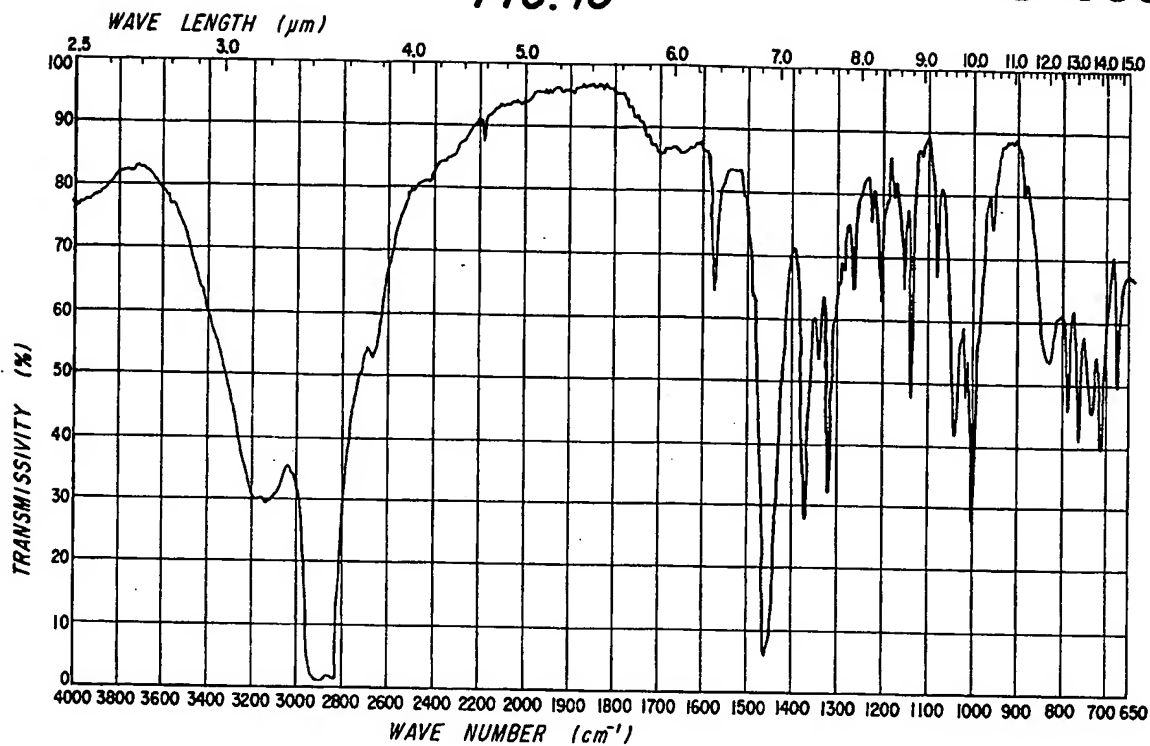
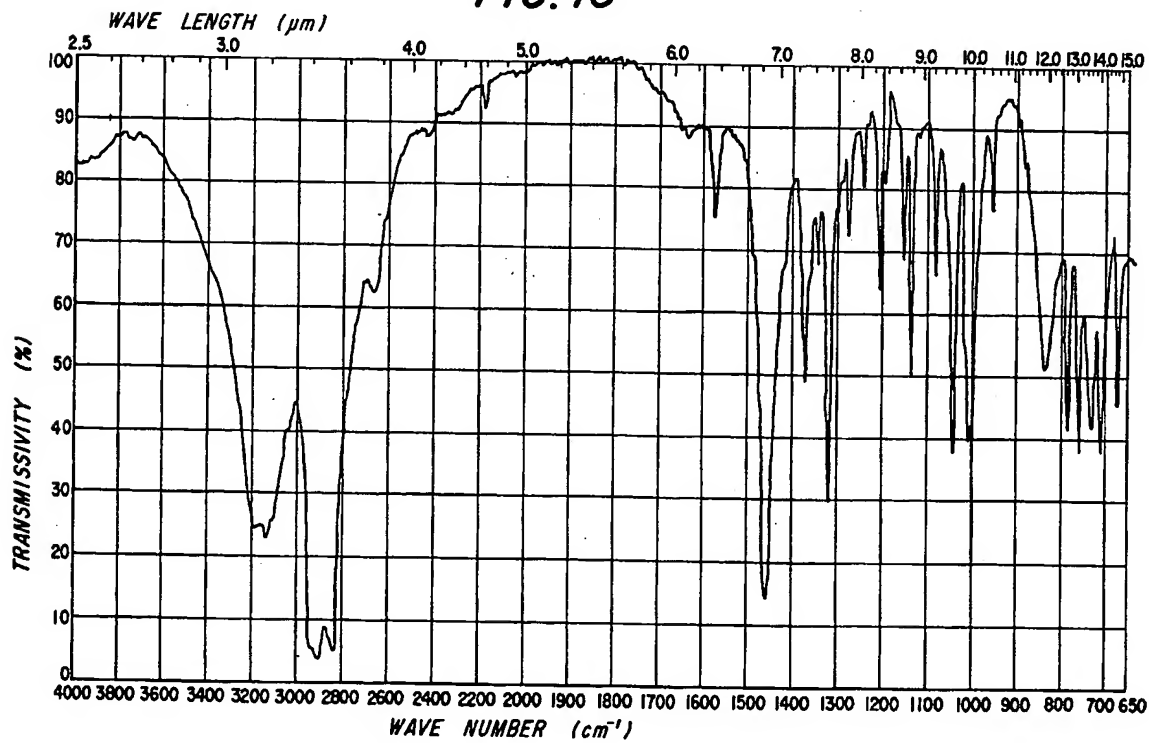


FIG. 16



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FIG. 17

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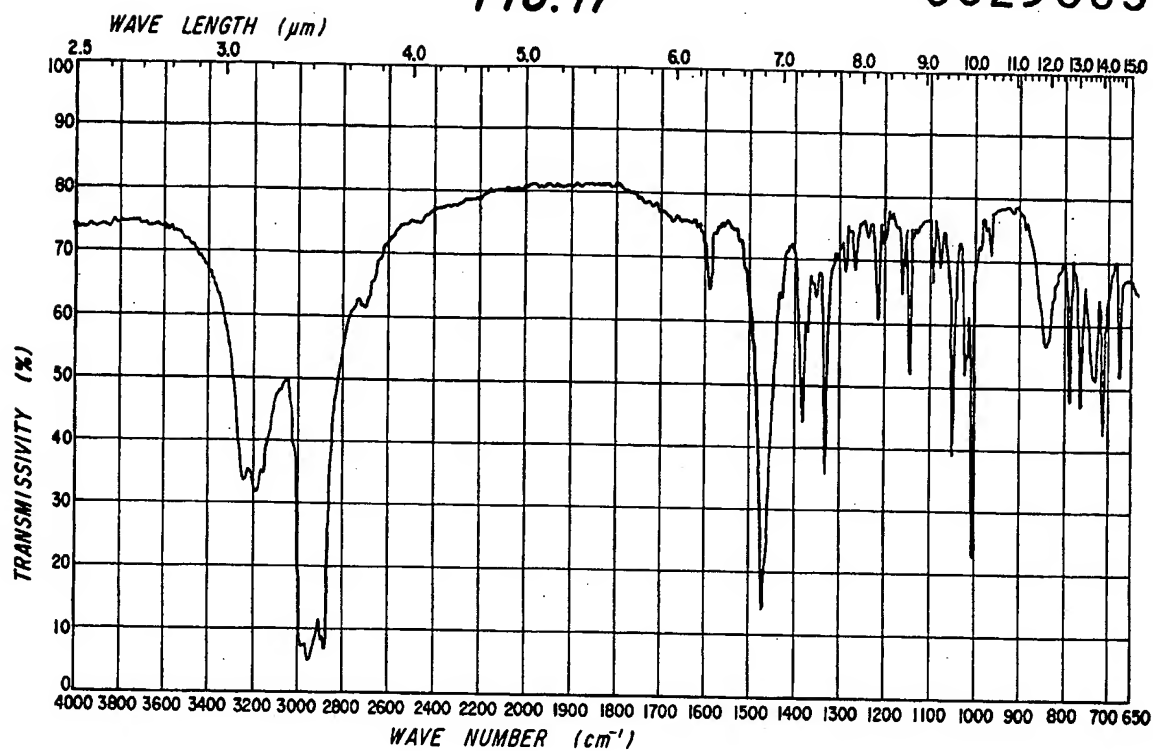
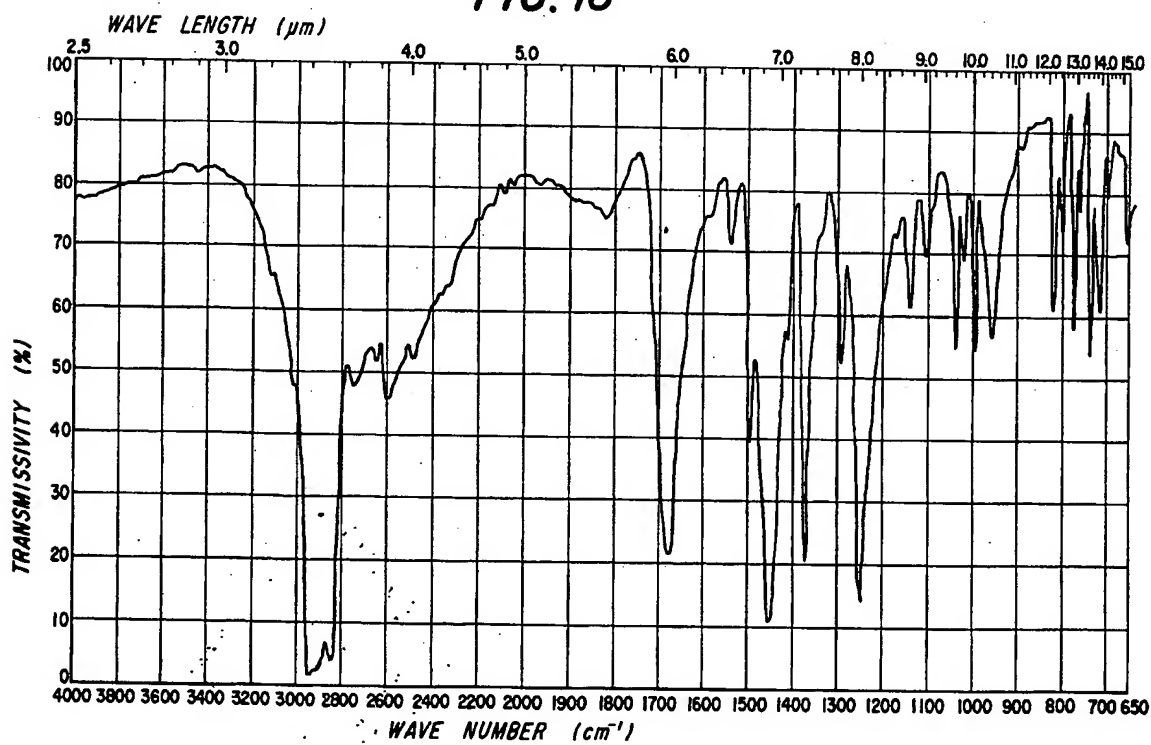


FIG. 18



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FIG. 19

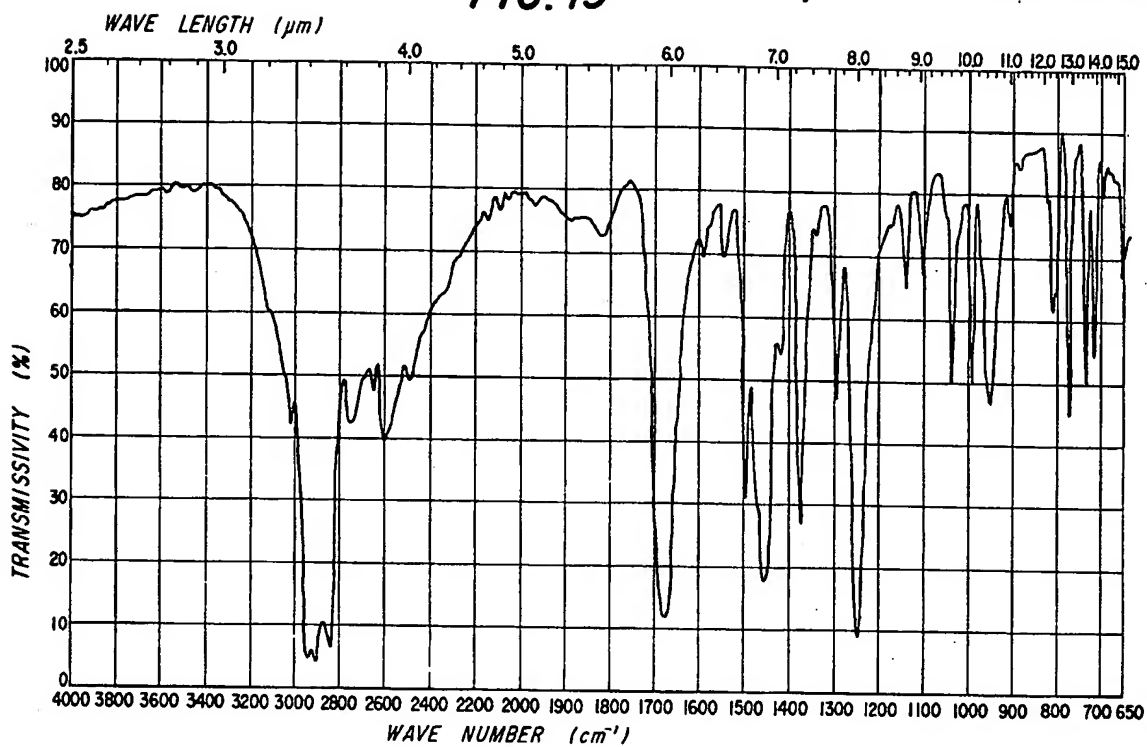
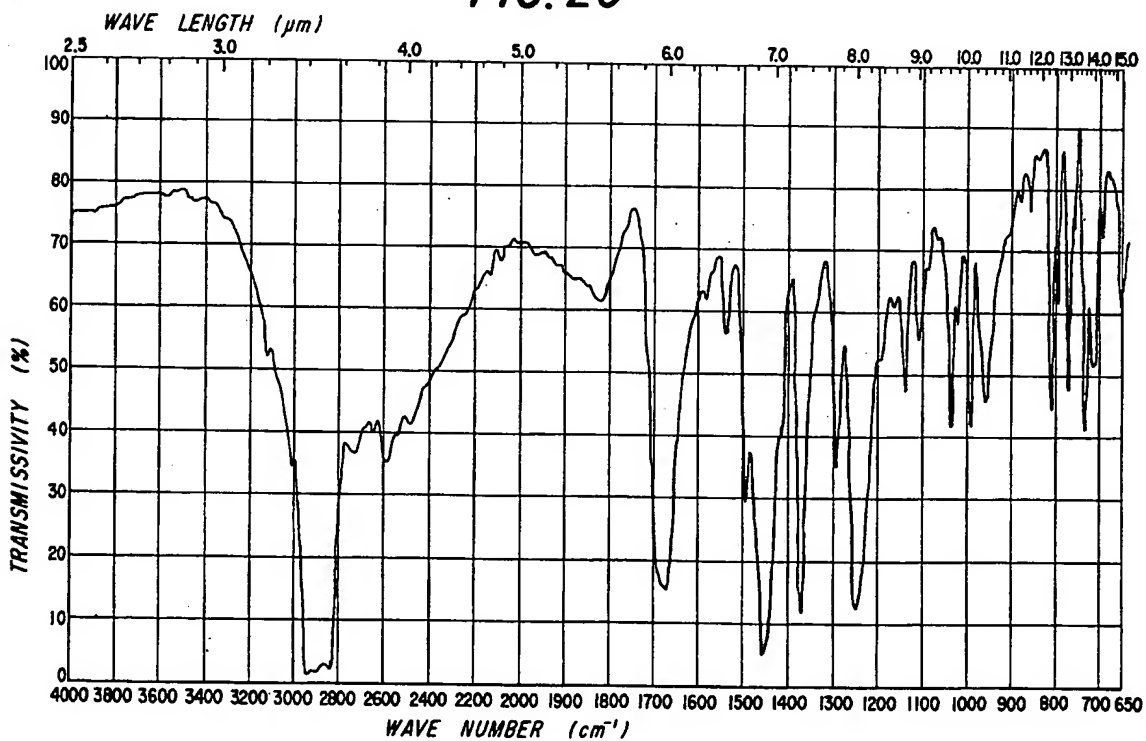


FIG. 20



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FIG. 21

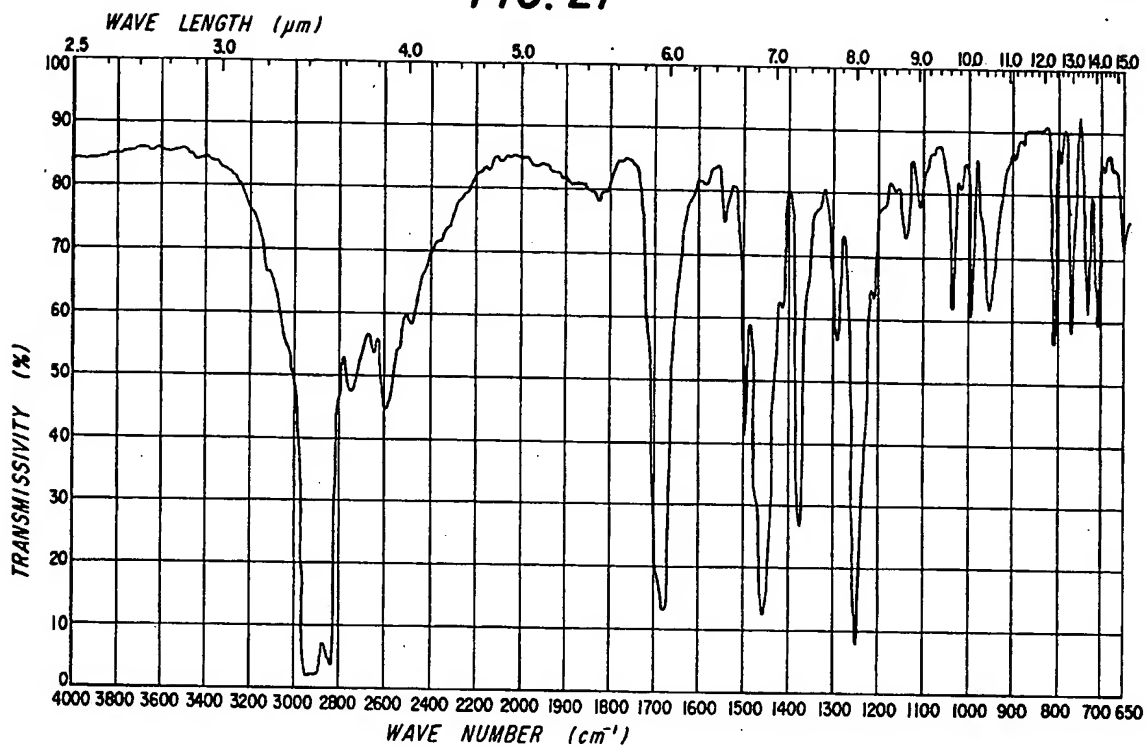


FIG. 22

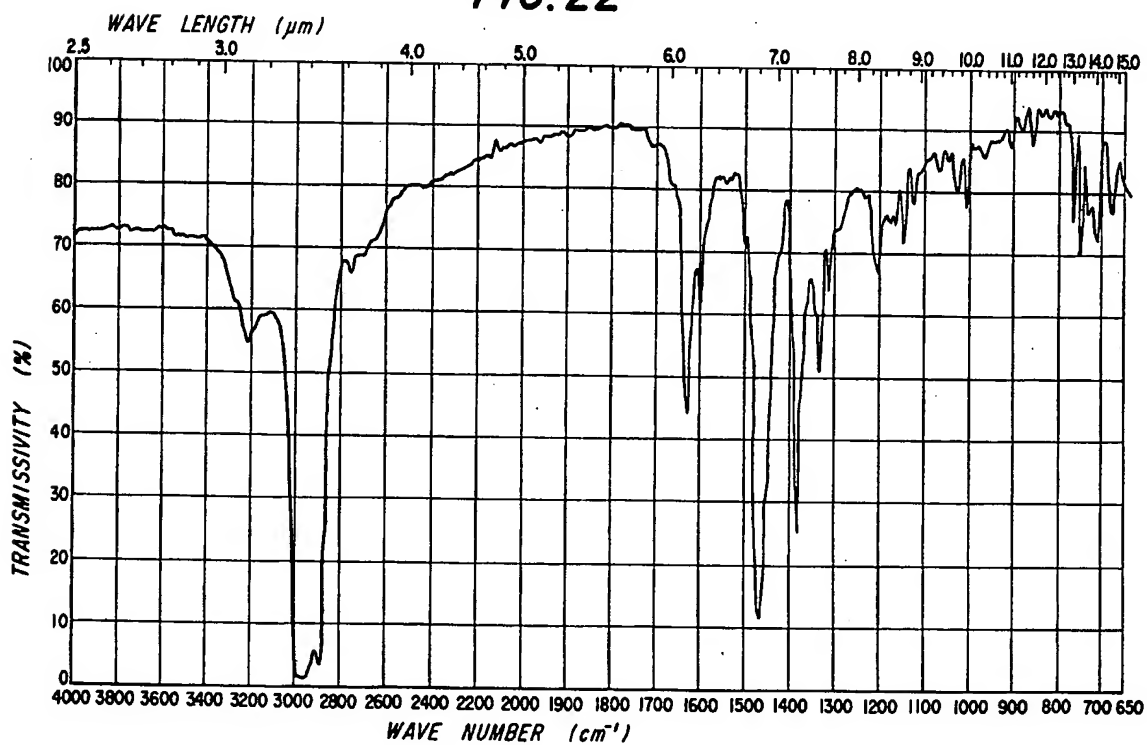


FIG. 23

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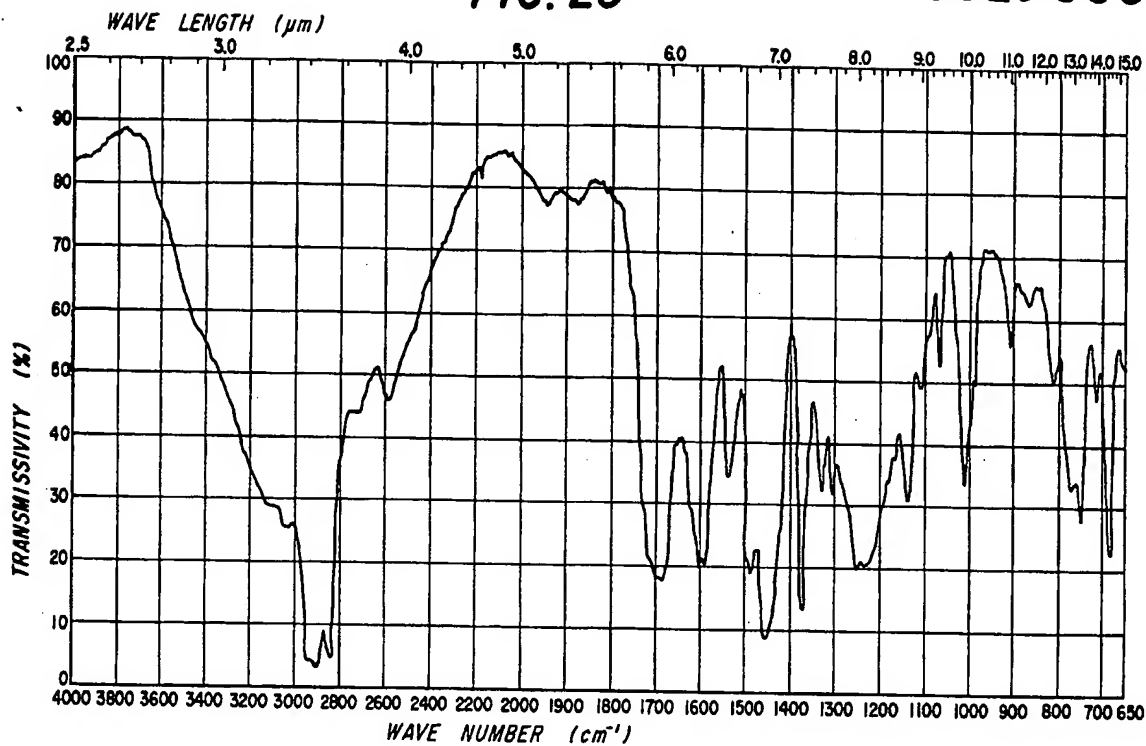
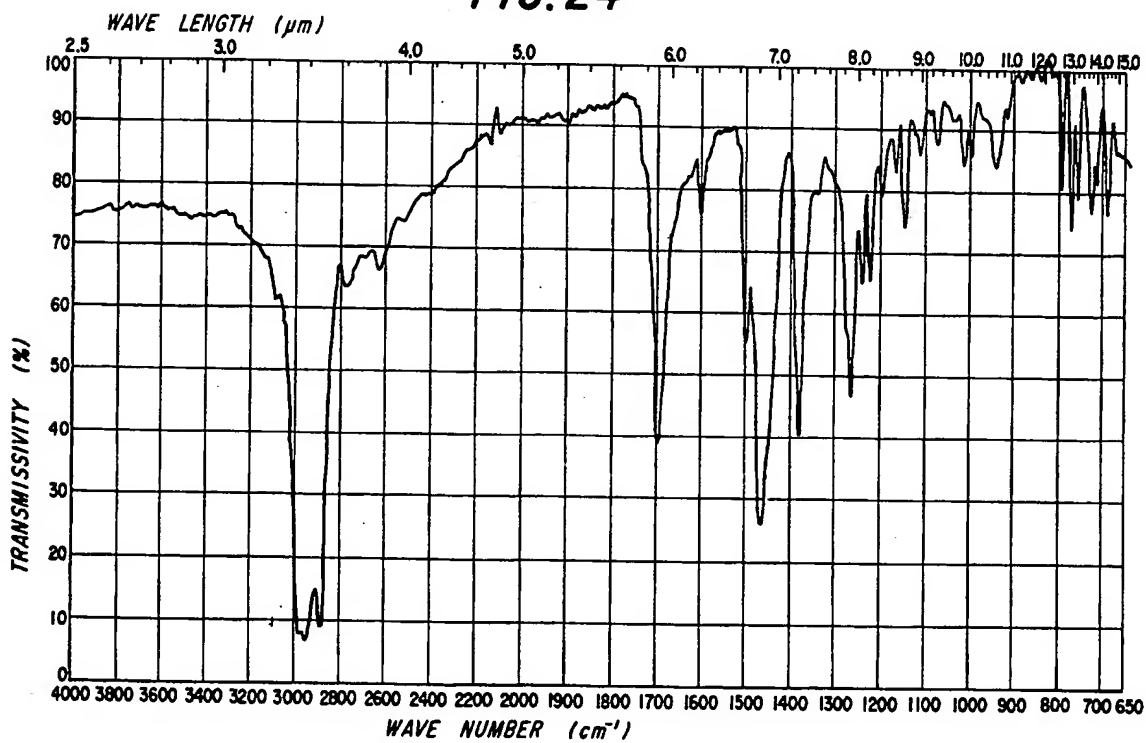


FIG. 24

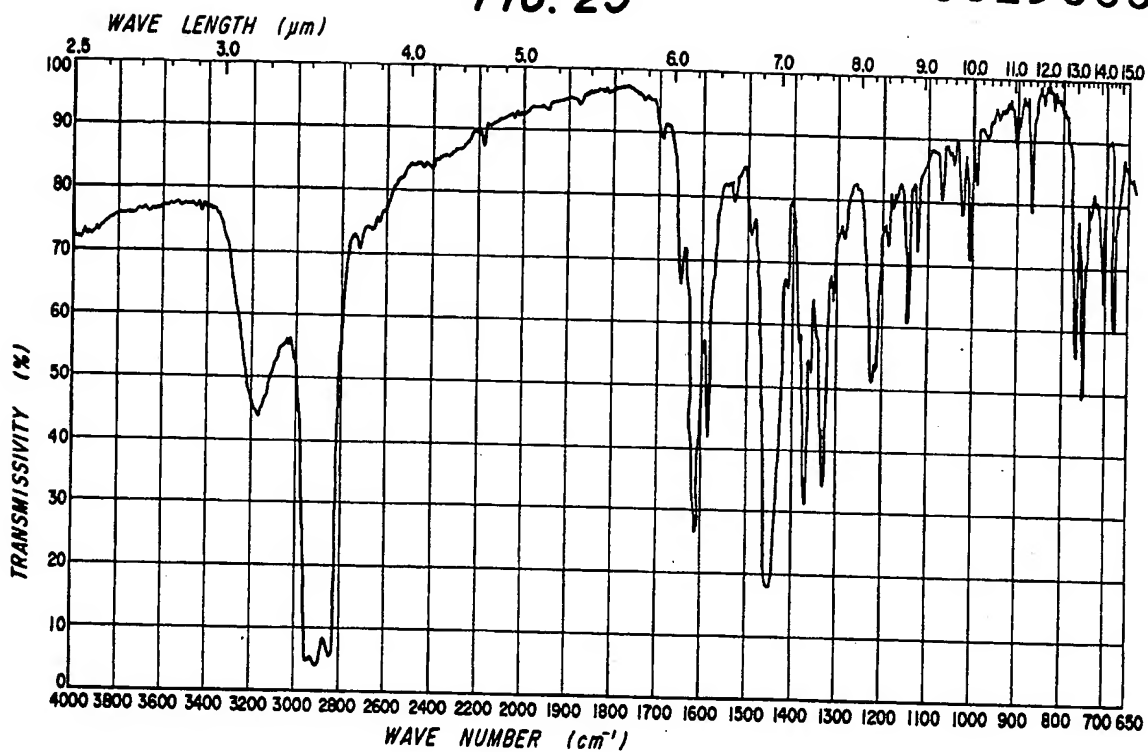


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FIG. 25

0029363





European Patent
Office

EUROPEAN SEARCH REPORT

Application number
EP 80304196.0
0029363

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl. 3)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	<u>GB - A - 1 048 104</u> (UPJOHN) + Totality + --	1,9	C 07 D 231/14 C 07 D 231/12 A 61 K 31/415
	<u>US - A - 3 899 508</u> (WIKEL) + Columns 1,2 + --	1,9	
	<u>US - A - 3 449 350</u> (WALKER) + Abstract + ----	1,9	
			TECHNICAL FIELDS SEARCHED (Int.Cl. 3)
			C 07 D 231/00 A 61 K 31/00
			CATEGORY OF CITED DOCUMENTS
			X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons
X	The present search report has been drawn up for all claims		&: member of the same patent family, corresponding document
Place of search VIENNA		Date of completion of the search 10-02-1981	Examiner LUX